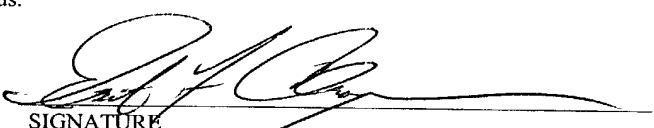


1007 Rec'd PCT/PTO 13 MAR 2002

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|---|-------------------------------------|---|-------------------------------------|--|--|
| FORM PTO-1390 REV. 2/01T | | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | | ATTORNEY'S DOCKET NUMBER 05281.0009 | |
| TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371 | | | | | |
| INTERNATIONAL APPLICATION NO. PCT/EP00/08833 | | INTERNATIONAL FILING DATE September 11, 2000 | | U.S. APPLICATION NO. (If known, see 37CFR 1.5) 10/070976 | |
| | | | | PRIORITY DATE CLAIMED September 17, 1999 | |
| TITLE OF INVENTION N-Substituted 4-Aminopteridines, A Process For Their Preparation And Their Use As Pharmaceuticals | | | | | |
| APPLICANT(S) FOR DO/EO/US Wolfgang PFLEIDERER, Harald SCHMIDT, Lothar FRÖHLICH, Peter KOTSONIS, and Shahriyar TAGHAVI-MOGHADAM | | | | | |
| Applicant(s) herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information: | | | | | |
| 1. | <input checked="" type="checkbox"/> | This is a FIRST submission of items concerning a filing under 35 U.S.C 371. | | | |
| 2. | <input type="checkbox"/> | This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. | | | |
| 3. | <input type="checkbox"/> | This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. | | | |
| 4. | <input checked="" type="checkbox"/> | The US has been elected by the expiration of 19 months from the priority date (Article 31). | | | |
| 5. | <input checked="" type="checkbox"/> | A copy of the International Application as filed (35 U.S.C. 371 (c)(2)). | | | |
| | | a. | <input checked="" type="checkbox"/> | is attached hereto (required only if not communicated by the International Bureau. | |
| | | b. | <input type="checkbox"/> | has been communicated by the International Bureau. | |
| | | c. | <input type="checkbox"/> | is not required, as the application was filed with the United States Receiving Office (RO/US). | |
| 6. | <input checked="" type="checkbox"/> | An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)). | | | |
| | | a. | <input checked="" type="checkbox"/> | is attached hereto. | |
| | | b. | <input type="checkbox"/> | has been previously submitted under 35 U.S.C. 154 (d)(4). | |
| 7. | <input checked="" type="checkbox"/> | Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)). | | | |
| | | a. | <input type="checkbox"/> | are attached hereto (required only if not communicated by the International Bureau). | |
| | | b. | <input type="checkbox"/> | have been communicated by the International Bureau. | |
| | | c. | <input type="checkbox"/> | have not been made; however, the time limit for making such amendments has NOT expired. | |
| | | d. | <input checked="" type="checkbox"/> | have not been made and will not be made. | |
| 8. | <input type="checkbox"/> | An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)). | | | |
| 9. | <input type="checkbox"/> | An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). | | | |
| 10. | <input checked="" type="checkbox"/> | An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)). | | | |
| Items 11 to 20 below concern document(s) or information included: | | | | | |
| 11. | <input checked="" type="checkbox"/> | Information Disclosure Statement under 37 CFR 1.97 and 1.98 | | | |
| 12. | <input type="checkbox"/> | An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. | | | |
| 13. | <input checked="" type="checkbox"/> | A FIRST preliminary amendment. | | | |
| 14. | <input type="checkbox"/> | A SECOND or SUBSEQUENT preliminary amendment. | | | |
| 15. | <input type="checkbox"/> | A Substitute specification. | | | |
| 16. | <input type="checkbox"/> | A change of power of attorney and/or address letter. | | | |
| 17. | <input type="checkbox"/> | A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825. | | | |
| 18. | <input type="checkbox"/> | A second copy of the published international application under 35 U.S.C. 154 (d)(4). | | | |
| 19. | <input type="checkbox"/> | A second copy of the English language translation of the international application 35 U.S.C. 154 (d)(4). | | | |
| 20. | <input checked="" type="checkbox"/> | Other items or information: | | | |
| | | a. | <input checked="" type="checkbox"/> | Copy of cover page of International Publication No. WO 01/21619 A1 | |
| | | b. | <input type="checkbox"/> | Copy of Notification of Missing Requirements. | |
| | | c. | <input type="checkbox"/> | | |

JC13 Rec'd PCT/PTO 13 MAR 2002

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|--|--------------|---|--------------|---|----|
| U.S. APPLICATION NO. (If known, see 37CFR 1.5) 10/070976 | | INTERNATIONAL APPLICATION NO. PCT/EP00/08833 | | ATTORNEY'S DOCKET NUMBER 05281.0009 | |
| 21. <input checked="" type="checkbox"/> The following fees are submitted: | | | | CALCULATIONS PTO USE ONLY | |
| BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)): | | | | | |
| Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00 | | | | | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 | | | | | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00 | | | | | |
| International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00 | | | | | |
| International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33 (1)-(4) \$100.00 | | | | | |
| ENTER APPROPRIATE BASIC FEE AMOUNT = | | | | \$ 890.00 | |
| Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)). | | | | \$ | |
| CLAIMS | NUMBER FILED | | NUMBER EXTRA | RATE | |
| Total Claims | 13 | - 20 = | | x \$18.00 | \$ |
| Independent Claims | 2 | -3 = | | x \$84.00 | \$ |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | | +\$280.00 | \$ |
| TOTAL OF THE ABOVE CALCULATIONS = | | | | \$ 890.00 | |
| <input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. | | | | \$ | |
| SUBTOTAL = | | | | \$ 890.00 | |
| Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest priority date (37 CFR 1.492(f)). | | | | \$ | |
| TOTAL NATIONAL FEE = | | | | 890.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21 (h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property. | | | | \$ | |
| TOTAL FEES ENCLOSED = | | | | \$ 890.00 | |
| | | | | Amount to be refunded: | \$ |
| | | | | charged: | \$ |
| a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>890.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>06-0916</u> . A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. | | | | | |
| NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status. | | | | | |
| SEND ALL CORRESPONDENCE TO: Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P. 1300 I Street, N.W. Washington, D.C. 20005-3315 | | | | | |
|  SIGNATURE | | | | Ernest F. Chapman. Reg. No. 25,961 | |
| DATED: March 13, 2002 | | | | NAME/REGISTRATION NO. | |

| | | | |
|--|---|---|--|
| FORM PTO-1390 REV. 2/01T | | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | ATTORNEY'S DOCKET NUMBER 05281.0009 |
| TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371 | | | U.S. APPLICATION NO. (If known, see 37CFR1.5) 10/070976 |
| INTERNATIONAL APPLICATION NO. PCT/EP00/08833 | INTERNATIONAL FILING DATE September 11, 2000 | PRIORITY DATE CLAIMED September 17, 1999 | |
| TITLE OF INVENTION N-Substituted 4-Aminopteridines, A Process For Their Preparation And Their Use As Pharmaceuticals | | | |
| APPLICANT(S) FOR DO/EO/US Wolfgang PFLEIDERER, Harald SCHMIDT, Lothar FRÖHLICH, Peter KOTSONIS, and Shahriyar TAGHAVI-MOGHADAM | | | |
| Applicant(s) herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information: | | | |
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| 3. | <input type="checkbox"/> | This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. | |
| 4. | <input checked="" type="checkbox"/> | The US has been elected by the expiration of 19 months from the priority date (Article 31). | |
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| | a. | <input checked="" type="checkbox"/> | is attached hereto (required only if not communicated by the International Bureau). |
| | b. | <input type="checkbox"/> | has been communicated by the International Bureau. |
| | c. | <input type="checkbox"/> | is not required, as the application was filed with the United States Receiving Office (RO/US). |
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| | a. | <input checked="" type="checkbox"/> | is attached hereto. |
| | b. | <input type="checkbox"/> | has been previously submitted under 35 U.S.C. 154 (d)(4). |
| 7. | <input checked="" type="checkbox"/> | Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3)). | |
| | a. | <input type="checkbox"/> | are attached hereto (required only if not communicated by the International Bureau). |
| | b. | <input type="checkbox"/> | have been communicated by the International Bureau. |
| | c. | <input type="checkbox"/> | have not been made; however, the time limit for making such amendments has NOT expired. |
| | d. | <input checked="" type="checkbox"/> | have not been made and will not be made. |
| 8. | <input type="checkbox"/> | An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)). | |
| 9. | <input type="checkbox"/> | An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)). | |
| 10. | <input checked="" type="checkbox"/> | An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)). | |
| Items 11 to 20 below concern document(s) or information included: | | | |
| 11. | <input checked="" type="checkbox"/> | Information Disclosure Statement under 37 CFR 1.97 and 1.98 | |
| 12. | <input type="checkbox"/> | An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. | |
| 13. | <input checked="" type="checkbox"/> | A FIRST preliminary amendment. | |
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| 15. | <input type="checkbox"/> | A Substitute specification. | |
| 16. | <input type="checkbox"/> | A change of power of attorney and/or address letter. | |
| 17. | <input type="checkbox"/> | A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825. | |
| 18. | <input type="checkbox"/> | A second copy of the published international application under 35 U.S.C. 154 (d)(4). | |
| 19. | <input type="checkbox"/> | A second copy of the English language translation of the international application 35 U.S.C. 154 (d)(4). | |
| 20. | <input checked="" type="checkbox"/> | Other items or information: | |
| | a. | <input checked="" type="checkbox"/> | Copy of cover page of International Publication No. WO 01/21619 A1 |
| | b. | <input type="checkbox"/> | Copy of Notification of Missing Requirements. |
| | c. | <input type="checkbox"/> | |

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JC13 Rec'd PCT/PTO 13 MAR 2002

PATENT

Customer No. 22,852

Attorney Docket No. 05281.0009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
)
Wolfgang PFLEIDERER et al) Group Art Unit: To Be Assigned
)
Serial No.: To Be Assigned) Examiner: To Be Assigned
)
Filed: Herewith)
)
For: N-Substituted 4-Aminopteridines,)
A Process For Their Preparation)
And Their Use As)
Pharmaceuticals)
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to the examination of the above application, please amend this application as follows:

IN THE SPECIFICATION:

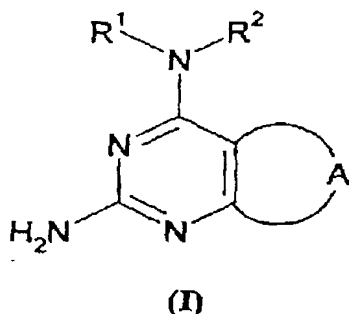
Page 1, after the title, please insert the following first paragraph:

-- This application is a national stage filing of International Application No. PCT/EP00/08833, filed September 11, 2000. This application also claims the benefit of priority under 35 U.S.C. § 119(a) to German Patent Application No. 199 44 767.5, filed on September 17, 1999. --

IN THE CLAIMS:

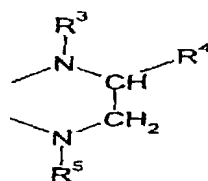
Please cancel claim 10, amend claims 1-9 and 11-12, and add new claims 13 and 14 as follows:

1. (Amended) A compound of formula I

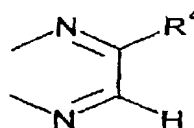


in which

A is



or



R^1 is hydrogen, C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^1 is unsubstituted or substituted with at least one substituent chosen from R^6 ,

R^2 is C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^2 is unsubstituted or substituted with at least one substituent chosen from R^6 ,

or R^1 and R^2 , together with the nitrogen atom bearing them, form a 3-8-membered ring, wherein said 3-8-membered ring optionally comprises 0, 1 or 2 further heteroatoms chosen from N, O, and S, and wherein said 3-8-membered ring is unsubstituted or substituted by at least one radical,

R^3 is hydrogen, -CO-alkyl, -CO-alkylaryl or -CO-aryl,

R^4 is C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl, arylalkyl, -CO-O-alkyl, -CO-O-aryl, -CO-alkyl -CO-aryl, wherein R^4 is unsubstituted or substituted with at least one substituent chosen from R^7 ,

R^5 is hydrogen, -CO-alkyl, -CO-alkylaryl or -CO-aryl,

R^6 is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹,

R^7 is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹,

R^8 is hydrogen or C₁-C₂₀-alkyl, and

R^9 is hydrogen, C₁-C₂₀-alkyl or aryl,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio.

2. (Amended) The compound as claimed in claim 1, in which

R^1 is hydrogen, (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, cycloalkylalkyl, aryl, (C₁-C₃)-alkylaryl or arylalkyl, wherein R^1 is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R^6

R^2 is (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, cycloalkylalkyl, aryl or (C₁-C₃)-alkylaryl, wherein R^2 is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R^6

or R^1 and R^2 , together with the nitrogen atom bearing them, form a 3-8-membered ring, wherein said 3-8-membered ring optionally comprises 0, 1 or 2 further heteroatoms chosen from N, O, and S and wherein said 3-8-membered ring is unsubstituted or substituted by at least one radical,

R^3 is hydrogen, -CO-(C₁-C₇)-alkyl, -CO-(C₁-C₃)-alkylaryl or -CO-aryl,

R^4 is (C₁-C₁₀)-alkyl, aryl, (C₁-C₃)-alkylaryl, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -CO-(C₁-C₅)-alkyl or -CO-aryl, wherein R^4 is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R^7

R^5 is hydrogen, -CO-(C₁-C₇)-alkyl, -CO-(C₁-C₃)-alkylaryl or -CO-aryl,

R^6 is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹,

R^7 is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹,

R^8 is hydrogen or (C₁-C₅)-alkyl, and

R^9 is hydrogen, (C₁-C₅)-alkyl or phenyl,

wherein each aryl group is chosen from phenyl, naphthyl and heteroaryl groups,

wherein said phenyl, naphthyl and heteroaryl groups are unsubstituted groups or substituted groups which are substituted by at least one substituent chosen from halogen, (C₁-C₅)-alkyl or phenyl, -OH, -O-(C₁-C₅)-alkyl, (C₁-C₂)-alkylenedioxy, -N⁸R⁹, -NO₂, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -S(O)_n-(C₁-C₅)-alkyl, and -SO₂-NR⁸R⁹,

wherein said heteroaryl groups are 5- to 7-membered unsaturated heterocycles comprising at least one heteroatom chosen from O, N, and S, and

wherein n is 0, 1 or 2,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio.

3. (Amended) The compound as claimed in claim 1, in which

R¹ is hydrogen, unsubstituted (C₂-C₄)-alkyl, substituted (C₂-C₄)-alkyl which is substituted by at least one R⁶, or (C₁-C₂)-alkylaryl,

R² is unsubstituted (C₂-C₄)-alkyl, substituted (C₂-C₄)-alkyl which is substituted by at least one R⁶, cyclohexylmethyl or (C₁-C₂)-alkylaryl,

or R¹ and R², together with the nitrogen atom bearing them, form a 5-7-membered ring wherein said 5-7-membered ring optionally comprises an additional heteroatom chosen from N, O, and S,

R³ is hydrogen, -CO-(C₁-C₃)-alkyl or -CO-aryl,

R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, wherein R⁴ is unsubstituted or substituted with at least one substituent chosen from R⁷,

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH, and

R⁷ is -OH, (C₁-C₁₀)-alkyloxy, phenoxy or oxo,

wherein each aryl group is chosen from phenyl, thienyl, furyl and pyridyl,

wherein said phenyl, thienyl, furyl and pyridyl groups are unsubstituted groups or substituted groups which are substituted by at least one substituent chosen from (C₁-C₃)-alkyl, halogen, (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio.

4. (Amended) The compound as claimed in claim 1, in which

R¹ is arylmethyl,

R² is arylmethyl or cyclohexylmethyl,

or R¹ and R², together with the nitrogen atom bearing them, form a pyrrolidine, piperidine, morpholine, dimethylmorpholine, thiomorpholine, or N-(C₁-C₂)-alkylpiperazine ring,

R³ is hydrogen,

R⁴ is alkyl or 1,2-dihydroxypropyl,

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH, and

R⁷ is -OH, decyloxy or phenoxy,

wherein each aryl group is chosen from unsubstituted phenyl or substituted phenyl, which is substituted by at least one substituent chosen from (C₁-C₃)-alkyl, halogen and (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio.

5. (Amended) The compound as claimed in claim 1, which is a tetrahydropteridine wherein R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, and wherein said R⁴ is unsubstituted or substituted with at least one substituent chosen from R⁷.

6. (Amended) The compound as claimed in claim 1, which is a pteridine wherein

R¹ and R² are each, independently alkyl or aryl, or

R¹ is hydrogen and R² is cycloalkyl or cycloalkylalkyl, and

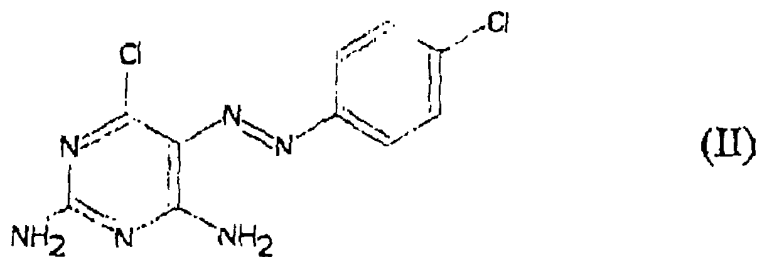
wherein R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, wherein said R⁴ is unsubstituted or substituted with at least one substituent chosen from R⁷.

7. (Amended) A pharmaceutical comprising at least one of the compounds as claimed in claim 1 and at least one additional ingredient chosen from conventional excipients additives and further active ingredients.

8. (Amended) A method of treating or preventing strokes, pathological falls in blood pressure, ulcerative colitis, transplant rejection reactions, nephritis, reperfusion damage, infarct damage, cardiomyopathy, Alzheimer's disease, epilepsy, migraine and neuritis of varying etiology comprising administration of at least one pharmaceutical of claim 7 to a patient in need thereof.

9. (Amended) A method of inhibiting NO synthase comprising administration of at least one pharmaceutical of claim 7 to a patient in need thereof.

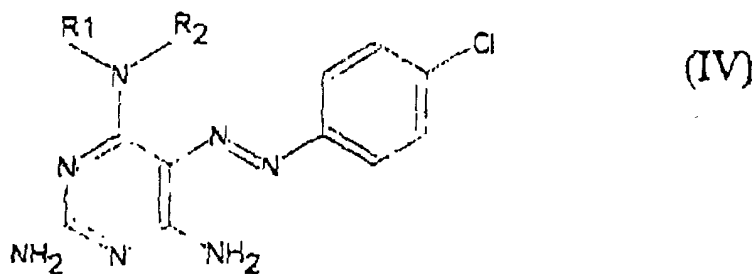
11. (Amended) A process for preparing the compound as claimed in claim 1 comprising reacting a compound of formula II



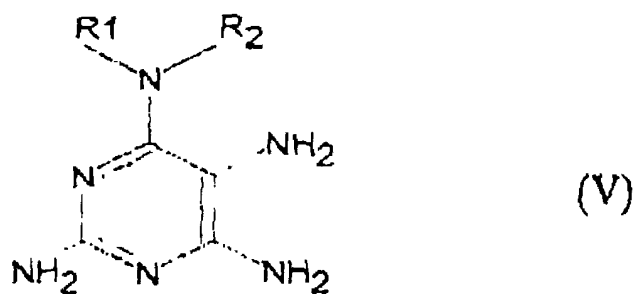
with a compound of formula III



which results in a compound of formula IV



wherein the compound of formula IV is converted to a compound of formula V by catalytic hydrogenation

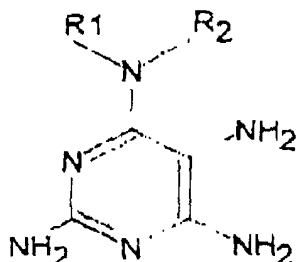


and wherein a compound of formula V is reacted with a compound of the formula VI



to give a compound of formula I.

12. (Amended) A compound of the formula V



(V),

in which

R¹ is hydrogen, C₁-C₂₀-alkyl, C₂-C₂₀-alkenyl, C₂-C₂₀-alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R¹ is unsubstituted or substituted with at least one substituent chosen from R⁶,

R² is C₁-C₂₀-alkyl, C₂-C₂₀-alkenyl, C₂-C₂₀-alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R² is unsubstituted or substituted with at least one substituent chosen from R⁶,

or R¹ and R², together with the nitrogen atom bearing them, form a 3-8-membered ring, wherein said 3-8 membered ring optionally comprises 0, 1 or 2 further heteroatoms chosen from N, O, and S and wherein said 3-8-membered ring is unsubstituted or substituted by at least one substituent chosen from R⁶, and

R⁶ is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹

R⁸ is hydrogen or C₁-C₂₀-alkyl, and

R⁹ is hydrogen, C₁-C₂₀-alkyl or aryl,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio.

- -13. The process for preparing the compound as claimed in claim 12, further comprising converting the compound of formula I by derivatization into a physiologically acceptable salt, hydrate, ester or adduct of the compound of formula I or into another compound of formula I.

14. The process of claim 13, wherein said derivatization is acylation. - -

REMARKS

The amendments to the claims are to matters of form directed to bringing the claims in conformance with U.S. patent practice. The claims were not narrowed by these amendments. As such, these amendments raise no issue of new matter and Applicants respectfully request their entry.

If there is any fee due in connection with the filing of this Preliminary Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

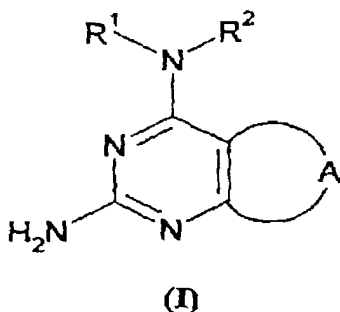
Dated: March 12, 2002

By: 

Anthony C. Tridico
Reg. No. 45,958

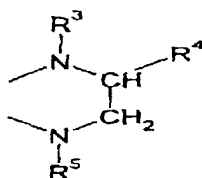
APPENDIX TO THE PRELIMINARY AMENDMENT

1. (Amended) **A compound of** [Compounds of the] formula I

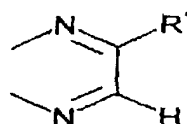


in which

A is [a bridge of the formula]



or



R^1 is hydrogen, C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^1 is unsubstituted or substituted with at least one substituent chosen from R^6 [where the organic radicals may be substituted by one or more substituents R^6],

R^2 is [, independently of R^1 ,] C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^2 is unsubstituted or substituted with at least one substituent chosen from R^6 [where the organic radicals may be substituted by one or more substituents R^6],

or R^1 and R^2 [may], together with the nitrogen atom bearing them, form a 3-8-membered ring, wherein said 3-8-membered ring optionally comprises [which may optionally contain] 0, 1 or 2 further heteroatoms chosen from [the series] N, O, and S, and [which is optionally substituted by one or more radicals] wherein said 3-8-membered ring is unsubstituted or substituted by at least one radical,

R^3 is hydrogen, -CO-alkyl, -CO-alkylaryl or -CO-aryl,

R⁴ is C₁-C₂₀-alkyl, C₂-C₂₀-alkenyl, C₂-C₂₀-alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, [or] alkylaryl, arylalkyl, -CO-O-alkyl, -CO-O-aryl, -CO-alkyl -CO-aryl, [where the organic radicals may be substituted by one or more substituents R⁷] **wherein R⁴ is unsubstituted or substituted with at least one substituent chosen from R⁷**,

R⁵ is[, independently of R³,] hydrogen, -CO-alkyl, -CO-alkylaryl or -CO-aryl,

R⁶ is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, **or** -SO₂-NR⁸R⁹,

R⁷ [has, independently of R⁶, one of the meanings of R⁶,] **is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹**,

R⁸ is hydrogen or C₁-C₂₀-alkyl, **and**

R⁹ is hydrogen, C₁-C₂₀-alkyl or aryl,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio. [in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts, hydrates and esters.]

2. (Amended) **The compound as claimed in claim 1** [Compounds of the formula I as claimed in claim 1], in which

R¹ is hydrogen, (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, cycloalkylalkyl, aryl [or] (C₁-C₃)-alkylaryl or arylalkyl, [where the alkyl radicals may be substituted by one or more substituents R⁶,] **wherein R¹ is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R⁶**

R² is[, independently of R¹,] (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, cycloalkylalkyl, aryl or (C₁-C₃)-alkylaryl, [where the alkyl radicals may be substituted by one or more substituents R⁶,] **wherein R² is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R⁶**

or R¹ and R² [may], together with the nitrogen atom bearing them, form a 3-8-membered ring, **wherein said 3-8-membered ring optionally comprises** [which may optionally contain] 0, 1 or 2 further heteroatoms **chosen** from [the series] N, O, **and** S and [which is optionally substituted by one or more radicals] **and wherein said 3-8-membered ring is unsubstituted or substituted by at least one radical,**

R³ is hydrogen, -CO-(C₁-C₇)-alkyl, -CO-(C₁-C₃)-alkylaryl or -CO-aryl,

R⁴ is (C₁-C₁₀)-alkyl, aryl [or] (C₁-C₃)-alkylaryl, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -CO-(C₁-C₅)-alkyl or -CO-aryl, [where the alkyl radicals may be substituted by one or more substituents R⁷,] **wherein R⁴ is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R⁷**

R⁵ [has, independently of R³, one of the meanings of R³,] is hydrogen, -CO-(C₁-C₇)-alkyl, -CO-(C₁-C₃)-alkylaryl or -CO-aryl,

R⁶ is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹,

R⁷ [has, independently of R⁶, one of the meanings of R⁶,] is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹,

R⁸ is hydrogen or (C₁-C₅)-alkyl, and

R⁹ is hydrogen, (C₁-C₅)-alkyl or phenyl,

wherein each aryl group is chosen from phenyl, naphthyl [or] and heteroaryl groups,

wherein said phenyl, naphthyl and heteroaryl groups are unsubstituted groups or substituted groups which are substituted by at least one substituent chosen from [all of which may be substituted by one or more identical or different substituents from the series] halogen, (C₁-C₅)-alkyl or phenyl, -OH, -O-(C₁-C₅)-alkyl, (C₁-C₂)-alkylenedioxy, -N⁸R⁹, -NO₂, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -S(O)_n-(C₁-C₅)-alkyl, and -SO₂-NR⁸R⁹,

wherein said heteroaryl groups are [is a] 5- to 7-membered unsaturated heterocycles [which contains one or more] comprising at least one heteroatom chosen from [the series] O, N, and S, and

wherein n is 0, 1 or 2,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio. [in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts, hydrates and esters.]

3. (Amended) The compound as claimed in claim 1 [Compound of the formula I as claimed in claim 1], in which

R¹ is hydrogen, unsubstituted (C₂-C₄)-alkyl, substituted (C₂-C₄)-alkyl which [may be] is substituted by [one or more substituents] at least one R⁶, or (C₁-C₂)-alkylaryl,

R² is unsubstituted (C₂-C₄)-alkyl, substituted (C₂-C₄)-alkyl which [may be] is substituted by [one or more substituents] at least one R⁶, [or] cyclohexylmethyl or (C₁-C₂)-alkylaryl,

or R¹ and R² [form], together with the nitrogen atom bearing them, form a 5-7-membered ring [which optionally contains no or another] wherein said 5-7-membered ring optionally comprises an additional heteroatom chosen from [the series] N, O, and S,

R³ is hydrogen, -CO-(C₁-C₃)-alkyl or -CO-aryl,

R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, **wherein R⁴ is unsubstituted or substituted with at least one substituent chosen from [each of which may be substituted by one or more substituents] R⁷,**

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH, **and**

R⁷ is -OH, (C₁-C₁₀)-alkyloxy, phenoxy or oxo,

wherein each aryl group is chosen from phenyl, thienyl, furyl [or] **and** pyridyl,

wherein said phenyl, thienyl, furyl and pyridyl groups are unsubstituted groups or substituted groups which are substituted by at least one substituent chosen from [each of which may be substituted by one or more substituents from the series] (C₁-C₃)-alkyl, halogen, (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy, [and]

[R⁸ and R⁹ have the meanings stated in claim 1],

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio. [in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts, hydrates and esters.]

4. (Amended) **The compound as claimed in claim 1** [Compounds of the formula I as claimed in claim 1], in which

R¹ is arylmethyl, [and]

R² is arylmethyl or cyclohexylmethyl,

or R¹ and R² [form], together with the nitrogen atom bearing them, **form** a pyrrolidine, piperidine, morpholine, dimethylmorpholine, thiomorpholine, or N-(C₁-C₂)-alkylpiperazine ring,

R³ is hydrogen,

R⁴ is alkyl or 1,2-dihydroxypropyl,

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH, **and**

R⁷ is -OH, decyloxy [and] **or** phenoxy,

wherein each aryl group is chosen from unsubstituted phenyl or substituted phenyl, which is substituted by at least one substituent chosen from [which may be substituted by one or more substituents from the series] (C₁-C₃)-alkyl, halogen and (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy, [and]

[R⁸ and R⁹ have the meanings stated in claim 1,]

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio. [in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts, hydrates and esters.]

5. (Amended) **The compound as claimed in claim 1** [Compounds of the formula I as claimed in claim 1], which is a tetrahydropteridine [in which] **wherein** R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, **and wherein said R⁴ is unsubstituted or substituted with at least one substituent chosen from R⁷.** [each of which may be substituted by one or more substituents R⁷.]

6. (Amended) **The compound as claimed in claim 1** [Compounds of the formula I as claimed in claim 1], which is a pteridine [in which] **wherein**

R¹ and R² are **each, independently** alkyl **or** [and/or] aryl, or

[in which] R¹ is hydrogen and R² is cycloalkyl or cycloalkylalkyl, and

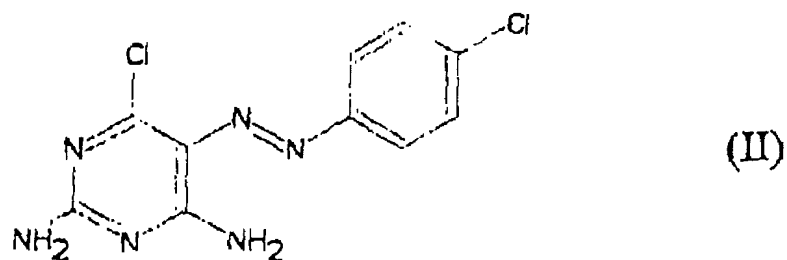
[in which] **wherein** R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, **wherein said R⁴ is unsubstituted or substituted with at least one substituent chosen from R⁷.** [each of which may be substituted by one or more substituents R⁷.]

7. (Amended) A pharmaceutical comprising **at least one of the compounds as claimed in claim 1** [a compound of the formula I as claimed in claim 1 in addition to] **and at least one additional ingredient chosen from** conventional excipients [and] additives and [optionally] further active ingredients.

8. (Amended) [A pharmaceutical as claimed in claim 7 for the therapy and prophylaxis of] **A method of treating or preventing** strokes, pathological falls in blood pressure, [in particular in septic shock and in cancer therapy with cytokines,] ulcerative colitis, transplant rejection reactions, nephritis, reperfusion damage, infarct damage, cardiomyopathy, Alzheimer's disease, epilepsy, migraine **or** [and] neuritis of varying etiology **comprising administration of at least one pharmaceutical of claim 7 to a patient in need thereof.**

9. (Amended) [A pharmaceutical as claimed in claim 7 as] **A method of inhibiting** [inhibitor of] NO synthase **comprising administration of at least one pharmaceutical of claim 7 to a patient in need thereof.**

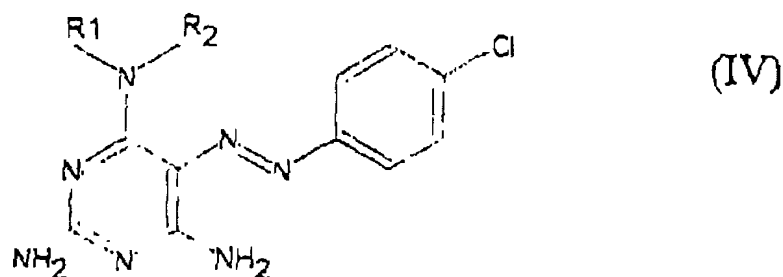
11. (Amended) A process for preparing **the compound as claimed in claim 1** **comprising** [a compound of the formula I as claimed in claim 1, by] reacting a compound of [the] formula II



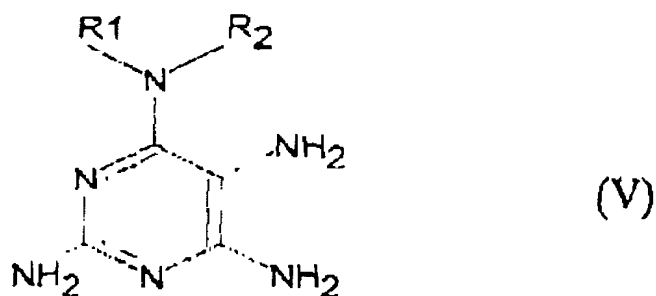
with a compound of [the] formula III



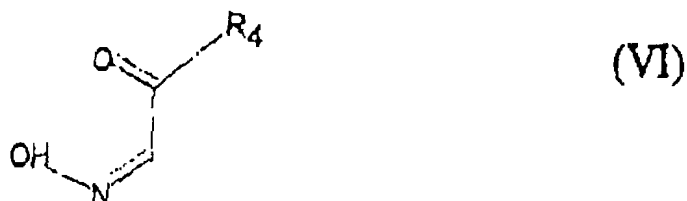
[to give a] which results in a compound of [the] formula IV



[and converting the latter by] wherein the compound of formula IV is converted to a compound of formula V by catalytic hydrogenation [into a compound of the formula V]

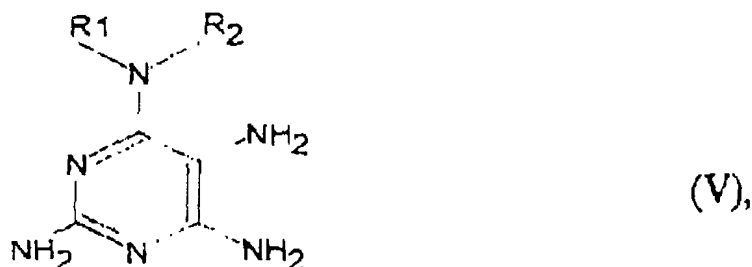


and wherein a compound of formula V [which] is reacted with a compound of the formula VI



to give a compound of formula I [which can be converted by suitable derivatization, preferably acylation, into the desired compound of the formula I or its physiologically acceptable salts, hydrates, esters and adducts, and in which the substituents have the meanings stated in claims 1 to 3].

12. (Amended) A compound of the formula V



in which

R^1 [has the meaning defined in claim 1, and] is hydrogen, C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^1 is unsubstituted or substituted with at least one substituent chosen from R^6 ,

R^2 is [independently of R^1] C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, [or] cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^1 is unsubstituted or substituted with at least one substituent chosen from R^6 [where the organic radicals may be substituted by one or more substituents R^6],

or R^1 and R^2 [may], together with the nitrogen atom bearing them, form a 3-8-membered ring [which may], wherein said 3-8 membered ring optionally comprises [contains] 0, 1 or 2 further heteroatoms chosen from [the series] N, O, and S and [which is optionally substituted by one or more radicals R^6] wherein said 3-8-membered ring is unsubstituted or substituted by at least one substituent chosen from R^6 , and

R^6 [has the meaning defined in claim 1] is -F, -OH, -O-(C_1 - C_{10})-alkyl, -O-phenyl, -O-CO-(C_1 - C_{10})-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C_1 - C_5)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C_1 - C_5)-alkyl, -CO-O-aryl, -S(O)_n-(C_1 - C_5)-alkyl, or -SO₂-NR⁸R⁹

R^8 is hydrogen or C_1 - C_{20} -alkyl, and

R^9 is hydrogen, C_1 - C_{20} -alkyl or aryl,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio..

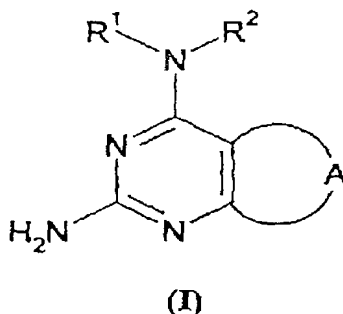
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TRANSLATION OF THE

Annexes (amended sheets) to the Preliminary Examination Report

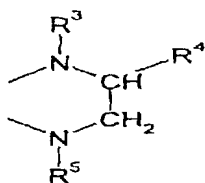
Patent Claims filed with letter of September 14, 2001

1. Compounds of the formula I

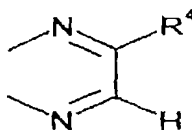


in which

A is a bridge of the formula



or



R¹ is hydrogen, C₁-C₂₀-alkyl, C₂-C₂₀-alkenyl, C₂-C₂₀-alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, where the organic radicals may be substituted by one or more substituents R⁶,

R² is, independently of R¹, C₁-C₂₀-alkyl, C₂-C₂₀-alkenyl, C₂-C₂₀-alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, where the organic radicals may be substituted by one or more substituents R⁶,

R¹ and R² may, together with the nitrogen atom bearing them,
form a 3-8-membered ring which may optionally contain 0,
1 or 2 further heteroatoms from the series N, O, S and
5 which is optionally substituted by one or more radicals,

R³ is hydrogen, -CO-alkyl, -CO-alkylaryl or -CO-aryl,

10 R⁴ is C₁-C₂₀-alkyl, C₂-C₂₀-alkenyl, C₂-C₂₀-alkynyl, cycloalkyl
with three to eight ring carbon atoms, cycloalkenyl with
three to eight ring carbon atoms, cycloalkylalkyl with
five to six ring carbon atoms, aryl or alkylaryl,
arylalkyl, -CO-O-alkyl, -CO-O-aryl, -CO-alkyl -CO-aryl,
15 where the organic radicals may be substituted by one or
more substituents R⁷,

R⁵ is, independently of R³, hydrogen, -CO-alkyl,
-CO-alkylaryl or -CO-aryl,

20 R⁶ is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-
alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-
alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -
CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, -SO₂-NR⁸R⁹,

25 R⁷ has, independently of R⁶, one of the meanings of R⁶,

R⁸ is hydrogen or C₁-C₂₀-alkyl,

30 R⁹ is hydrogen, C₁-C₂₀-alkyl or aryl,

in all its stereoisomeric and tautomeric forms and mixtures
thereof in all ratios, and its physiologically acceptable
salts, hydrates and esters.

35 2. Compounds of the formula I as claimed in claim 1, in which

R¹ is hydrogen, (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, cycloalkylalkyl, aryl or (C₁-C₃)-alkylaryl or arylalkyl, where the alkyl radicals may be substituted by one or more substituents R⁶,

R² is, independently of R¹, (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl, cycloalkylalkyl, aryl or (C₁-C₃)-alkylaryl, where the alkyl radicals may be substituted by one or more substituents R⁶,

R¹ and R² may, together with the nitrogen atom bearing them, form a 3-8-membered ring which may optionally contain 0, 1 or 2 further heteroatoms from the series N, O, S and which is optionally substituted by one or more R⁶ radicals,

R³ is hydrogen, -CO-(C₁-C₇)-alkyl, -CO-(C₁-C₃)-alkylaryl or -CO-aryl,

R⁴ is (C₁-C₁₀)-alkyl, aryl or (C₁-C₃)-alkylaryl, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -CO-(C₁-C₅)-alkyl or -CO-aryl, where the alkyl radicals may be substituted by one or more substituents R⁷,

R⁵ has, independently of R³, one of the meanings of R³,

R⁶ is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, -SO₂-NR⁸R⁹,

R⁷ has, independently of R⁶, one of the meanings of R⁶,

R⁸ is hydrogen or (C₁-C₅)-alkyl,

R⁹ is hydrogen, (C₁-C₅)-alkyl or phenyl,

aryl is phenyl, naphthyl or heteroaryl, all of which may be substituted by one or more identical or different substituents from the series halogen, (C₁-C₅)-alkyl or phenyl, -OH, -O-(C₁-C₅)-alkyl, (C₁-C₂)-alkylenedioxy, -N⁸R⁹, -NO₂, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -S(O)_n-(C₁-C₅)-alkyl, -SO₂-NR⁸R⁹,

heteroaryl is a 5- to 7-membered unsaturated heterocycle which contains one or more heteroatoms from the series O, N, S,

n is 0, 1 or 2,

in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios and its physiologically acceptable salts, hydrates and esters.

3. Compound of the formula I as claimed in claim 1, in which

R¹ is hydrogen, (C₂-C₄)-alkyl which may be substituted by one or more substituents R⁶, or (C₁-C₂)-alkylaryl,

R² is (C₂-C₄)-alkyl which may be substituted by one or more substituents R⁶, or cyclohexylmethyl or (C₁-C₂)-alkylaryl,

or R¹ and R² form, together with the nitrogen atom bearing them, a 5-7-membered ring which optionally contains no or another heteroatom from the series N, O, S,

R³ is hydrogen, -CO-(C₁-C₃)-alkyl or -CO-aryl,

R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, each of which may be substituted by one or more substituents R⁷,

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH,

R⁷ is -OH, (C₁-C₁₀)-alkyloxy, phenoxy or oxo,

aryl is phenyl, thienyl, furyl or pyridyl, each of which may be substituted by one or more substituents from the series (C₁-C₃)-alkyl, halogen, (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy, and

R⁸ and R⁹ have the meanings stated in claim 1,

in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios and its physiologically acceptable salts, hydrates and esters.

4. Compounds of the formula I as claimed in claim 1, in which

R¹ is arylmethyl and

R² is arylmethyl or cyclohexylmethyl,

or R¹ and R² form, together with the nitrogen atom bearing them, a pyrrolidine, piperidine, morpholine, dimethylmorpholine, thiomorpholine, or N-(C₁-C₂)-alkylpiperazine ring,

R³ is hydrogen,

R⁴ is alkyl or 1,2-dihydroxypropyl,

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH,

R⁷ is -OH, decyloxy and phenoxy,

aryl is phenyl which may be substituted by one or more substituents from the series (C₁-C₃)-alkyl, halogen and (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy, and

5 R⁸ and R⁹ have the meanings stated in claim 1,

in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios and its physiologically acceptable salts, hydrates and esters.

10

5. Compounds of the formula I as claimed in claim 1, which is a tetrahydropteridine in which R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, each of which may be substituted by one or more substituents R⁷.

15

6. Compounds of the formula I as claimed in claim 1, which is a pteridine in which R¹ and R² are alkyl and/or aryl, or in which R¹ is hydrogen and R² is cycloalkyl or cycloalkylalkyl, and in which R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, each of
20 which may be substituted by one or more substituents R⁷.

7. A pharmaceutical comprising a compound of the formula I as claimed in claim 1 in addition to conventional excipients and additives and optionally further active ingredients.

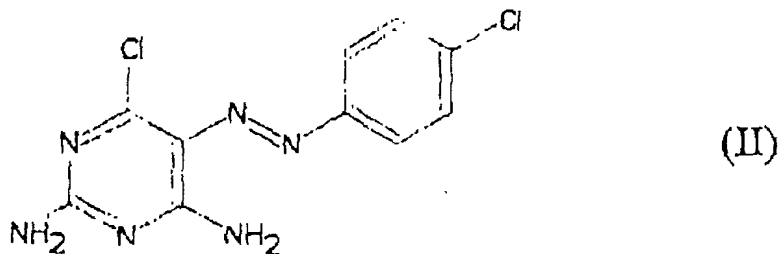
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8. A pharmaceutical as claimed in claim 7 for the therapy and prophylaxis of strokes, pathological falls in blood pressure, in particular in septic shock and in cancer therapy with cytokines, ulcerative colitis, transplant rejection
30 reactions, nephritis, reperfusion damage, infarct damage, cardiomyopathy, Alzheimer's disease, epilepsy, migraine and neuritis of varying etiology.

9. A pharmaceutical as claimed in claim 7 as inhibitor of NO
35 synthase.

10. The use of the pharmaceutical as claimed in claim 9 for diagnostic purposes.

11. A process for preparing a compound of the formula I as
5 claimed in claim 1, by reacting a compound of the formula II

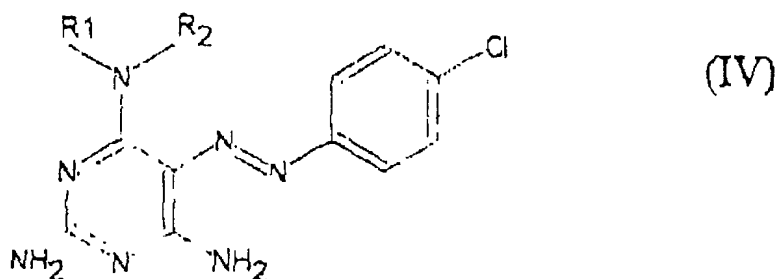


with a compound of the formula III

10

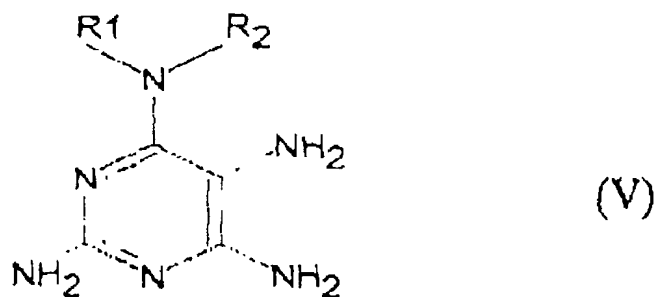


to give a compound of the formula IV



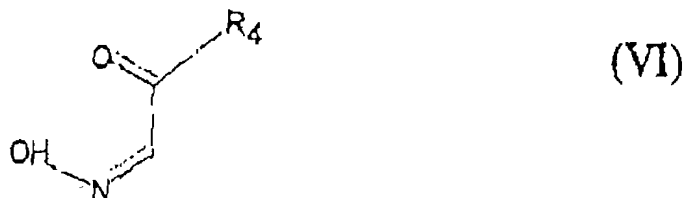
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and converting the latter by catalytic hydrogenation into a compound of the formula V



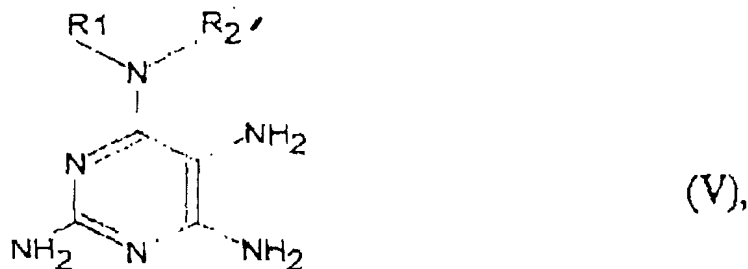
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which is reacted with a compound of the formula VI



to give a compound of the formula I, which can be converted by suitable derivatization, preferably acylation, into the desired compound of the formula I or its physiologically acceptable salts, hydrates, esters and adducts, and in which the substituents have the meanings stated in claims 1 to 3.

12. A compound of the formula V



in which R^1 has the meaning defined in claim 1, and $R^{2'}$ is, independently of R^1 , C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, [or] cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, [where the organic radicals may be substituted by one or more substituents R^6]

R^1 and $R^{2'}$ may, together with the nitrogen atom bearing them, form a 3-8-membered ring [which may] optionally contain 0, 1 or 2 further heteroatoms from the series N, O, S and [which is] optionally substituted by one or more radicals R^6 , and

R^6 has the meaning defined in claim 1.

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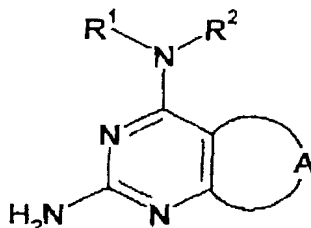
N-Substituted 4-aminopteridines, a process for their preparation and their use as pharmaceuticals

Description

5

The present invention relates to N-substituted 4-amino-
pteridines of the following general formula, a process
for their preparation and their use for the prevention
and treatment of diseases caused by a disturbed nitric
oxide balance.

10



Nitric oxide (NO) is a ubiquitous bearer of
physiological and pathophysiological functions
(S. Moncada et al. *Pharmacol. Rev.* 43 (1991), 109-142).
It has a relaxant effect on the smooth muscles of
vessels and, in this way, is crucially involved in the
regulation of blood pressure and the proliferation of
vessel wall cells; it controls, via inhibition of
platelet aggregation, the coagulation of blood and is
involved as neuromodulator in the brain and spinal
cord. NO likewise functions as messenger in the NANC
nerves of the peripheral nervous system. The cytotoxic
effect of NO is utilized by macrophages and a large
number of other cells for defence against infections
but also plays a part in the inflammatory reaction and
autoimmune reaction.

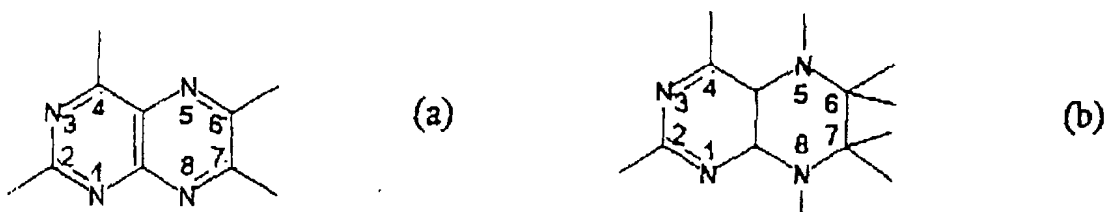
Endogenous NO is produced with the aid of three
different NO synthase isoenzymes from arginine
(Kershaw, *Ann. Rep. Med. Chem.* 27 (1992) 69). All the
isoenzymes require NADPH, flavin adenine dinucleotide,
flavin mononucleotide and tetrahydrobiopterin as

30

cofactors. They differ in their localization in the body, in their regulation by Ca^{2+} /calmodulin and in their inducibility by endotoxins and cytokines. The constitutive, calcium-dependent NO synthases are found, for example, in the endothelium (type III) and in the brain (type I) and are there involved in the regulation of blood pressure and coagulation and in conduction processes. The cytokine-inducible, calcium-independent isoform (type II) occurs in macrophages, smooth muscle cells and hepatocytes. It is able to produce relatively large amounts of NO over a long period and is thought to be responsible for inflammatory and autoimmune processes and the cytotoxic activity of macrophages.

A disturbed NO balance results in serious disorders and damages. Thus, excessive production of NO in septic or hemorrhagic shock leads to massive pathological falls in blood pressure. Excessive NO production is involved, for example, in the development of autoimmune diseases such as type 1 diabetes, and of atherosclerosis and is partly responsible for the glutamate-induced neurotoxicity following cerebral ischemia. High NO concentrations may in addition lead, through deamination of cytosine, to DNA damage and cancer. Selective inhibition of the NO synthases involved in the particular pathological states is therefore for the treatment or prevention of said diseases.

Only a few representatives of N-substituted 4-amino-pterins have been disclosed in the chemical literature to date. All these representatives contain either a substituent differing from hydrogen in the 7-position of the pterin framework or an aminobenzoylglutamate residue analogous to folic acid in the 6-position of the pterin framework (see formulae (a) and (b) below for the pterin framework).



Extremely little information is available about the pharmacological effect of N-substituted 4-aminopterins:

5 Dewey et al. (Biochem. Pharmacol. 23 (1974) 773) and Weinstock et al. (J. Med. Chem. 11 (1968) 573) report a potentially diuretic effect of 2,7-diamino-4-methylamino-6-phenylpteridine, Roth et al. (J. Am. Chem. Soc. 73 (1951) 1914) determined the antagonistic

10 effect of various folic acid-analogous (2-amino-4-alkylaminopteridin-6-ylmethyl)aminobenzoylglutamates on *S. faecalis* R. The effect of these derivatives, which is characterized by the authors as "weak", is likely to be attributable to a large extent to the presence of the

15 aminobenzoylglutamate, which is typical of such agents, in the 6-position of the pteridine.

There has likewise to date been only little discussion of the use of pterin analogues for inhibiting NO

20 synthase (NOS) in the literature. The majority of published pharmacological approaches to NOS inhibition are based on a competitive effect on the substrate binding site of the enzyme for L-arginine via substrate analogues (see, for example, E.S. Furfine et al. J. Biol. Chem. 269 (1994) 26677).

25

Further potential NO synthase inhibitors which have been discussed in the literature are N-iminoethyl-ornithine (Mc Call et al., Br. J. Pharmacol. 102 (1991)

30 234), aminoguanidine (T.P. Misko et al., Eur. J. Pharmacol., 233 (1993) 119, EP547588-A1) and 7-nitro-indazole (P.K. Moore et al., Br. J. Pharmacol. 108 (1993) 296).

The effect of simple 6R-5,6,7,8-tetrahydrobiopterin analogues (BH₄ analogues) on NO production has been investigated by Stuehr et al. (J. Biol. Chem. 264 (1989) 20496), Giovanelli et al. (Proc. Natl. Acad. Sci. 88 (1991) 7091), Mülsch and Busse (J. Cardiovasc. Pharmacol. 17 (1991) S52), Sakai et al. (Mol. Pharmacol. 43 (1992) 6), Werner et al. (FEBS Letters 305 (1992) 160), Wachter et al. (Biochem. J. 289 (1993) 357) and by Hevel and Marletta (Biochemistry 31 (1992) 7160). According to these, 6S-BH₄, 7-R/S-BH₄, 6-methyl-5,6,7,8-tetrahydropterin and dihydrobiopterin are able to partly replace the natural cofactor. Biopterin, 6,7-dimethyl-5,6,7,8-tetrahydropterin, tetrahydrofolic acid, dihydrofolic acid, folic acid, tetrahydro-neopterin, dihydroneopterin, neopterin, methotrexate, pterin, 6-hydroxymethylpterin, xanthopterin and isoxanthopterin showed no significant effects. Only with 5-deaza-6-methyl-5,6,7,8-tetrahydropterin was it possible to achieve a weak inhibition of NO synthase. Overfeld et al. (Br. J. Pharmacol., 107 (1992) 1008) observed inhibition of NO production in intact rat alveolar macrophages by BH₄ and sepiapterin, which is presumably based on a feedback mechanism. Pterin-6-carboxylic acid showed no effect in these tests.

Bömmel et al. (J. Biol. Chem. 273 (1998) 33142 and Portland Press Proc. 15 (1998) 57) used pterins and photolabile pterin derivatives for characterizing the tetrahydrobiopterin binding site of NO synthase.

The use of pteridinones for inhibiting NO synthase is disclosed in WO-A-94/14780. EP-A-0,760,818 and EP-A-0,760,664 describe the use of a number of differently substituted pteridines and tetrahydro-pteridines for inhibiting NO synthase. The pterins and pteridines described therein are, however, still in need of improvement in relation to some properties such as activity, selectivity for particularly NO synthase isoforms and solubility.

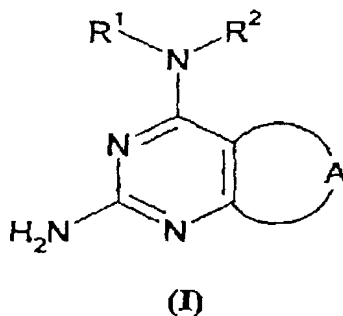
Pfeiffer et al. (Biochem. J. 328 (1997) 349) describe 4-aminobiopterin as inhibitor of NO synthase (Biochem. J., 328 (1997) 349). These compounds have, inter alia,
5 a free amino group in the 4-position and a side chain in the 6-position which is unaltered compared with the natural cofactor. Recently solved X-ray structures (B.R. Crane et al., Science 279 (1998) 2121) show interactions of these compounds with NO synthase.

10

It has now been found, surprisingly, that, in particular, pteridines whose amino group in the 4-position is substantially blocked by substituents, preferably by alkylation or dialkylation, and which
15 have in the 6-position a predominantly lipophilic group are potent inhibitors of NO synthase and, as such, can be used for the treatment of diseases associated with an increased NO level.

20 The pterins of the general formula I represent compared with the pterins disclosed in EP 0 760 818 and EP 0 760 664, a considerable and, in every respect, surprising advance especially in relation to the NO synthase-inhibiting effect, isoform selectivity and the
25 sustained improvement in the solubility properties.

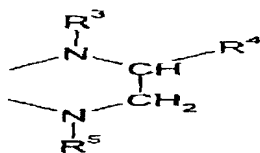
The present invention relates to compounds of the general formula I



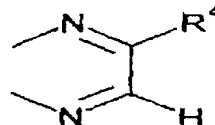
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where

A is a bridge of the form



or



R¹ is hydrogen, alkyl, alkenyl, alkynyl, preferably
 5 (C₁-C₁₀)-alkyl, cycloalkyl, cycloalkenyl,
 preferably (C₃-C₈)-cycloalkyl, cycloalkylalkyl,
 aryl, alkylaryl, preferably (C₁-C₃)-alkylaryl or
 arylalkyl, where the organic radicals, preferably
 the alkyl radicals, may be substituted by one or
 10 more substituents, preferably by substituents R⁶,

R² is, independently of R¹, alkyl, alkenyl, alkynyl,
 preferably (C₁-C₁₀)-alkyl, cycloalkyl,
 cycloalkenyl, preferably (C₃-C₈)-cycloalkyl,
 15 cycloalkylalkyl, aryl, alkylaryl, preferably (C₁-
 C₃)-alkylaryl, or arylalkyl, where the organic
 radicals, preferably the alkyl radicals, may be
 substituted by one or more substituents,
 preferably by substituents R⁶,

20

R¹ and R² may, together with the nitrogen atom bearing
 them, form a 3-8-membered ring which may
 optionally contain 0, 1 or 2 further heteroatoms
 from the series N, O, S and which is optionally
 25 substituted by one or more radicals, preferably R⁶
 radicals,

R³ is hydrogen, -CO-alkyl, preferably
 -CO-(C₁-C₇)-alkyl, -CO-alkylaryl, preferably
 30 -CO-(C₁-C₃)-alkylaryl or -CO-aryl,

R⁴ is alkyl, alkenyl, alkynyl, preferably
 (C₁-C₁₀)-alkyl, cycloalkyl, cycloalkenyl,
 preferably (C₃-C₈)-cycloalkyl, cycloalkylalkyl,

aryl or alkylaryl, preferably (C₁-C₃)-alkylaryl, arylalkyl, -CO-O-alkyl, preferably -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -CO-alkyl, preferably -CO-(C₁-C₅)-alkyl or -CO-aryl, where the
 5 organic radicals, preferably the alkyl radicals, may be substituted by one or more substituents, in particular by substituents R⁷,

R⁵ is, independently of R³, hydrogen, -CO-alkyl, preferably -CO-(C₁-C₇)-alkyl, -CO-alkylaryl, preferably -CO-(C₁-C₃)-alkylaryl or -CO-aryl,
 10

R⁶ is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, preferably -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, -SO₂-NR⁸R⁹,
 15

R⁷ has, independently of R⁶, one of the meanings of R⁶,
 20

R⁸ is hydrogen or alkyl, preferably (C₁-C₅)-alkyl,

R⁹ is hydrogen, alkyl, preferably (C₁-C₅)-alkyl or aryl, preferably phenyl,
 25

aryl is preferably phenyl, naphthyl or heteroaryl, each of which may be unsubstituted or substituted, for example may be substituted by one or more identical or different substituents from the series halogen, alkyl, preferably (C₁-C₅)-alkyl or phenyl, -OH, -O-alkyl, preferably -O-(C₁-C₅)-alkyl, alkylenedioxy, preferably (C₁-C₂)-alkylenedioxy, -N⁸R⁹, -NO₂, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -S(O)_n-(C₁-C₅)-alkyl, -SO₂-NR⁸R⁹,
 30
 35

heteroaryl is a 5- to 7-membered unsaturated heterocycle which contains one or more heteroatoms from the series O, N, S,

5 n is 0, 1 or 2,

in all their stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and their physiologically acceptable salts, hydrates and esters.

10

If groups or substituents occur more than once in the compounds of the formula I, they may all, independently of one another, have the stated meanings and may in each case be identical or different.

15

Alkyl radicals may be straight-chain or branched. This also applies if they are present in other groups, for example in alkoxy groups, alkoxycarbonyl groups or in amino groups, or if they are substituted. Alkyl radicals normally contain one to twenty carbon atoms, preferably one to ten carbon atoms.

20

Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of these radicals, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl.

25

Examples of alkenyl radicals are straight-chain or branched hydrocarbon radicals which contain one or more double bonds. Alkenyl radicals normally contain two to twenty carbon atoms and one or two double bonds, preferably two to ten carbon atoms and one double bond.

30

Examples of alkynyl radicals are straight-chain or branched hydrocarbon radicals which contain one or more triple bonds. Alkynyl radicals normally contain two to twenty carbon atoms and one or two triple bonds, preferably two to ten carbon atoms and one triple bond.

35

Examples of alkenyl radicals are the vinyl radical, the 2-propenyl radical (allyl radical), the 2-butenyl radical and the 2-methyl-2-propenyl radical.

5

Examples of alkynyl radicals are the ethynyl radical, the 2-propynyl radical (propargyl radical) or the 3-butenyl radical.

10 Cycloalkyl radicals are saturated cyclic hydrocarbons which normally contain three to eight ring carbon atoms, preferably five or six ring carbon atoms. Cycloalkyl radicals may in turn be substituted.

15 Examples of cycloalkyl radicals are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, all of which may also be substituted for example by one or more identical or different (C₁-C₄)-alkyl radicals, in particular by methyl. Examples of
20 such substituted cycloalkyl radicals are 4-methylcyclohexyl or 2,3-dimethylcyclopentyl.

Cycloalkenyl radicals are unsaturated cyclic hydrocarbons which normally contain three to eight ring
25 carbon atoms, preferably five or six ring carbon atoms. Cycloalkenyl radicals preferably have a double bond in the ring system. Cycloalkenyl radicals may in turn be substituted.

30 Cycloalkylalkyl radicals are saturated hydrocarbons which are derived from a cycloalkyl-substituted alkyl group. The cycloalkyl group normally has five to six ring carbon atoms. Examples of cycloalkylalkyl radicals are cyclopentylmethyl, cyclopentylethyl, cyclohexyl-
35 ethyl and, in particular, cyclohexylmethyl. Cycloalkyl-alkyl radicals may in turn be substituted.

Aryl is a carbocyclic or heterocyclic aromatic radical, preferably phenyl, naphthyl or heteroaryl. Aryl

radicals may be unsubstituted or substituted. Substituents are one or more identical or different monovalent organic radicals, for example or from the series halogen, alkyl, phenyl, -OH, -O-alkyl, 5 alkylenedioxy, -NR⁸R⁹, -NO₂, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -S(O)_n-(C₁-C₅)-alkyl, -SO₂-NR⁸R⁹.

Alkylaryl is an alkyl-substituted aryl radical, 10 preferably (C₁-C₃)-alkylaryl, in particular methylphenyl.

Arylalkyl is an aryl-substituted alkyl radical, preferably phenylmethyl or 2-phenylethyl.

15

Heteroaryl or a heterocyclic aromatic radical is preferably a 5- to 7-membered unsaturated heterocycle which has one or more heteroatoms from the series O, N, S.

20

Examples of heteroaryls from which the radicals occurring in compounds of the formula I may be derived are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-oxazole, 1,2-oxazole, 1,3-thiazole, 1,2-thiazole, tetrazole, 25 pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxan, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 30 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine or 1,3-thiazepine.

The radicals derived from the heterocycles may be 35 bonded via any suitable carbon atom. Nitrogen heterocycles which have a hydrogen atom (or a substituent) on a ring nitrogen atom, for example pyrrole, imidazole, etc, may also be bonded via a ring nitrogen atom, especially if the relevant nitrogen

heterocycle is bonded to a carbon atom. A thienyl radical may, for example, be in the form of a 2-thienyl radical or 3-thienyl radical, a furan radical in the form of a 2-furyl radical or 3-furyl radical, a pyridyl radical in the form of a 2-pyridyl radical, 3-pyridyl radical or 4-pyridyl radical.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

10

R^1 is preferably hydrogen, (C_2-C_4) -alkyl which may be substituted by one or more substituents R^6 , or (C_1-C_2) -alkylaryl, and R^1 is particularly preferably arylmethyl

15

R^2 is preferably (C_2-C_4) -alkyl which may be substituted by one or more substituents R^6 , or (C_1-C_2) -alkylaryl, and R^2 is particularly preferably arylmethyl

20

in addition, R^1 and R^2 preferably form, together with the nitrogen atom bearing them, a 5-7-membered ring which preferably contains no or only one other heteroatom from the series N, O, S. Very particularly preferred rings of this type are pyrrolidine, piperidine, morpholine, dimethylmorpholine, thiomorpholine or N- (C_1-C_2) -alkylpiperazine, where these rings themselves may also be substituted, for example by -OH, -O- (C_1-C_3) -alkyl, -NR⁸R⁹ or -COOH.

30

R^3 is preferably hydrogen, CO- (C_1-C_3) -alkyl or CO-aryl, and R^3 is very particularly preferably hydrogen.

35

R^4 is preferably aryl, (C_1-C_3) -alkyl which may be substituted by one or more substituents R^7 , or -CO-O-aryl. Particularly preferred R^4 radicals are aryl and 1,2-dihydroxypropyl.

R⁵ is preferably hydrogen.

5 R⁶ is preferably -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH.

R⁷ is preferably -OH, -O-(C₁-C₁₀)-alkyl, phenoxy, oxo, particularly preferably -OH, decyloxy and phenoxy.

10 aryl is preferably phenyl, thienyl, furyl and pyridyl, and phenyl is particularly preferred, all of which can be substituted as described. Preferred substituents are (C₁-C₃)-alkyl, halogen and (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy. The
15 preferred number of substituents on aryl radicals is 0, 1 or 2; phenyl substituents are preferably in the meta or para position, and in the case of two substituents in the 3 and 4 positions.

20 n is preferably 0 and 2

Concerning so-called structure-activity relations, it must be stated that in this connection in particular the 4- and the 6-positions of the pterin framework
25 appear to be of relevance. In the case of tetrahydropterins (compare formula (b)), for example large-volume substituents in the 6-position such as, for example, substituted phenyl, increase the activity of the agents. In the case of aromatic structures
30 (compare formula (a)), an increase in activity is observed preferentially when the amino substituent in the 4-position is dialkylated or diaralkylated and the 6-position is arylated.

35 The invention encompasses all possible enantiomers and diastereomers of the compounds of the general formula I, as well as mixtures of two or more stereoisomeric forms, for example mixtures of enantiomers and/or diastereomers, in all ratios.

The invention thus encompasses enantiomers in enantiopure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and
5 in the form of mixtures of the two enantiomers in all ratios. If a cis/trans isomerism is present, both the cis-form and the trans-form and mixtures of these forms in all ratios are encompassed by the invention. Individual stereoisomers can, if desired, be prepared
10 by fractionating a mixture by conventional methods, for example by chromatography or crystallization, by use of stereochemically pure starting materials in the synthesis or by stereoselective synthesis. A separation of stereoisomers may optionally be preceded by a
15 derivatization. The separation of the mixture of stereoisomers can take place at the stage of compounds of the formula I or at the stage of an intermediate during the synthesis. If mobile hydrogen atoms are present, the present invention also encompasses all
20 tautomeric forms of the compounds of the formula I.

The invention also encompasses the corresponding physiologically or toxicologically acceptable salts, in particular the pharmaceutically usable salts. Thus, the
25 compounds of the formula I which contain acidic groups may, for example, be in the form of alkali metal salts, alkaline earth metal salts or of ammonium salts and these groups can be used according to the invention. Examples of such salts are sodium salts, potassium
30 salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids.

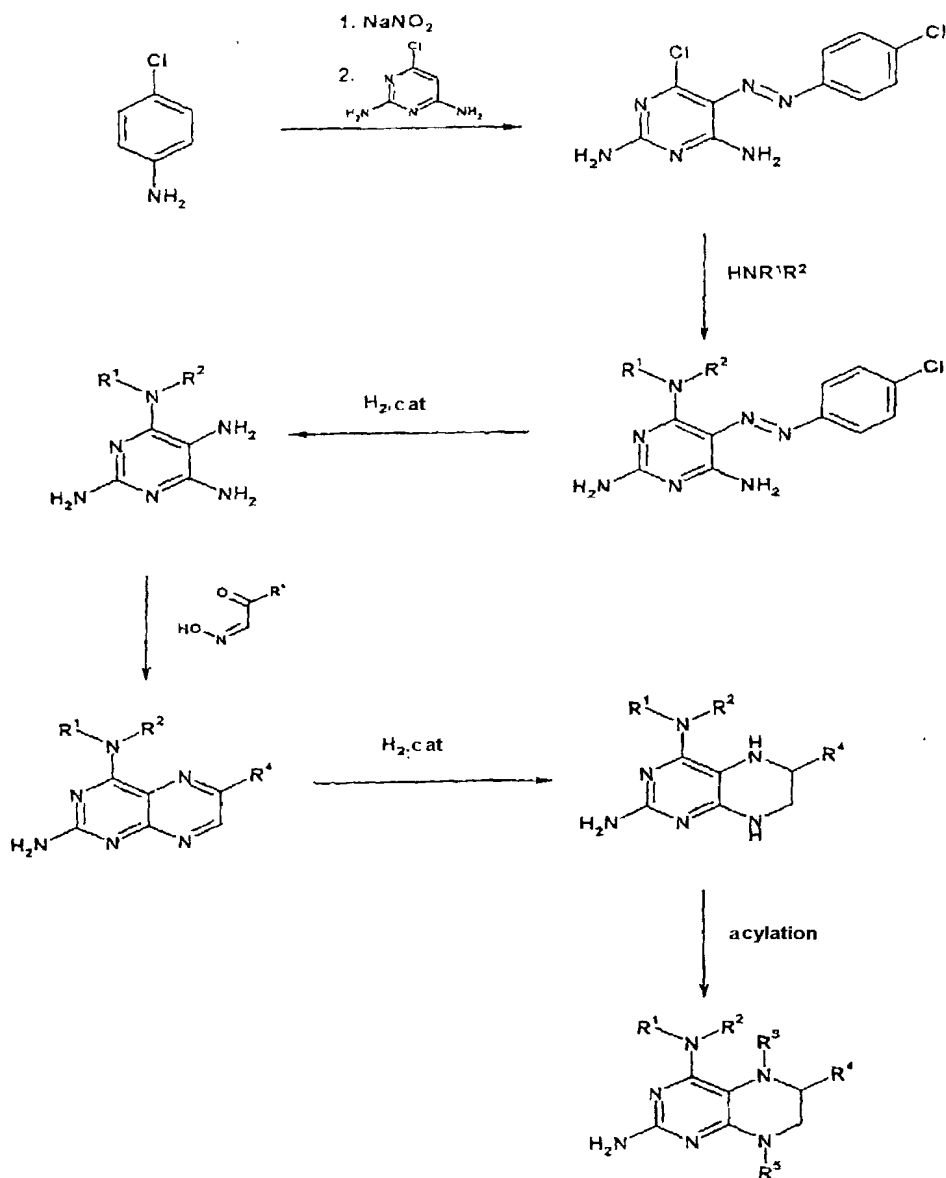
35 Compounds of the formula I which contain one or more basic, that is protonatable, groups may be in the form of their acid addition salts with physiologically acceptable inorganic or organic acids and used according to the invention, for example as salts with

hydrochloric acid, hydrobromic acid, phosphoric acid,
sulfuric acid, nitric acid, methanesulfonic acid,
p-toluenesulfonic acid, naphthalenedisulfonic acids,
oxalic acid, acetic acid, tartaric acid, lactic acid,
5 salicylic acid, benzoic acid, formic acid, propionic
acid, pivalic acid, diethylacetic acid, malonic acid,
succinic acid, pimelic acid, fumaric acid, maleic acid,
malic acid, sulfamic acid, phenylpropionic acid,
gluconic acid, ascorbic acid, isonicotinic acid, citric
10 acid, adipic acid etc.

If the compounds of the formula I contain both acidic
and basic groups in the molecule, the invention also
includes inner salts or betaines (zwitterions) in
15 addition to the salt forms described.

Salts can be obtained from compounds of the formula I
by conventional processes known to the skilled worker,
for example by combining with an organic or inorganic
20 acid or base in a solvent or dispersant, or else by
anion exchange or cation exchange from other salts. The
present invention further encompasses all solvates of
compounds of the formula I, for example hydrates or
adducts with alcohols, and derivatives of the compounds
25 of the formula I such as, for example, esters, and
prodrugs and active metabolites.

Compounds according to the invention of the general
formula I can be obtained as shown in the following
30 synthesis scheme



The scheme is explained in detail below:

- 5 To synthesize compounds of the general formula I, 2,6-diamino-4-chloro-5-p-chlorophenylazopyrimidine (II) as pure substance or in a solvent such as, for example, DMF, toluene or tetrahydrofuran is reacted with a 2-20-fold excess of an amine of the general formula HNR^1R^2
- 10 (III) at a temperature which is preferably between room temperature (RT) and the boiling point of the solvent. Alternatively, the reaction can also be carried out

with an equimolar amount of the amine in the presence of an auxiliary base such as, for example, triethylamine or Hünig base.

- 5 The resulting 2,6-diamino-4-(subst. amino)-5-p-chloro-phenylazopyrimidines (IV) are hydrogenated in a solvent such as, for example, methanol, ethanol or water, preferably in the presence of an acid such as, for example, HCl or acetic acid, or in the presence of a
10 base such as, for example, ammonia, with the aid of a catalyst such as, for example, Raney nickel, platinum dioxide or palladium on carbon under a pressure of between 1 and 200 atm of hydrogen.
- 15 The 2,5,6-triamino-(subst. amino)pyrimidines (V) obtained in this way are then mixed in a solvent such as, for example, methanol, ethanol, DMF or water with the particular glyoxal monoxime (VI) containing the radical R^4 , and this mixture is stirred until
20 conversion is complete at a temperature which is between RT and the boiling point of the solvent employed. After cooling, the suspension or solution is made basic with a base such as, for example, ammonia, and the precipitate which has separated out is filtered
25 off with suction, washed with water and dried.

A solution of the resulting pteridine is hydrogenated in a solvent such as THF, methanol or ethanol with the assistance of a catalyst such as, for example, Raney
30 nickel, platinum dioxide or palladium on carbon under a pressure of between 1 and 200 atm of hydrogen.

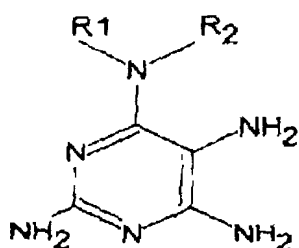
Further derivatization to introduce the substituents R^3 and/or R^4 can be carried out by standard processes for
35 acylations which are known to the skilled worker.

The abovementioned reactions for preparing 4-amino-pteridine derivatives are described in principle, for example, in WO-A-97/21711.

The present invention likewise relates to the above-mentioned process for preparing compounds of the formula I.

5

The present invention likewise relates to compounds of the formula V



(V),

10

In this, R¹ and R² have the meaning defined hereinbefore.

Diseases which are produced by an increased NO level and which thus can be treated according to the invention with compounds of the general formula I or which can be prevented using the latter are, in particular, pathological falls in blood pressure like those occurring in septic or hemorrhagic shock, in tumor therapy with cytokines or in cirrhosis of the liver, or autoimmune diseases such as type I diabetes, and atherosclerosis. In addition inflammatory diseases such as rheumatoid arthritis and, in particular, ulcerative colitis, and insulin-dependent diabetes mellitus and transplant rejection reactions.

The following disorders are also associated with an increased production of nitric oxide and can be treated according to the invention. In the cardiovascular system these are atherosclerosis, post-ischaemic reperfusion damage, myocarditis based on coxsackie virus infection and cardiomyopathy; in the central nervous system types of neuritis, encephalomyelitis, viral neurodegenerative disorders, Alzheimer's disease,

hyperalgesia, epilepsy and migraine; in the renal system acute renal failure and glomerulonephritis.

5 In addition, areas of application of compounds of the general formula I are also treatments in the region of the stomach and of the uterus/placenta and influencing the motility of sperm.

10 Compounds of the formula I and their physiologically acceptable salts, hydrates, esters and adducts can thus be used in animals, preferably in mammals, and in particular in humans, as pharmaceuticals on their own, or in mixtures with one another or together with other agents. The present invention therefore also relates in
15 particular to the use of compounds of the formula I and their physiologically acceptable salts, hydrates and esters for producing a medicament for the therapy or prophylaxis of the aforementioned pathological states, and to the use for producing a medicament for lowering
20 or normalizing an NO level.

The invention likewise relates to the use of the compounds of the formula I and their physiologically acceptable salts, hydrates and esters for inhibiting NO
25 synthase, to their use for the therapy or prophylaxis of the aforementioned pathological states and to their use for normalizing a disturbed NO balance.

Likewise encompassed are pharmaceuticals which comprise
30 the compounds of the formula I, their physiologically acceptable salts, esters and hydrates and esters on their own, in mixtures with one another or together with other agents in addition to conventional excipients and additives.

35 Examples of such other therapeutically active substances are: β -receptor blockers such as, for example, propanolol, pindolol, metoprolol; vasodilators such as, for example, carbocromen; sedatives such as,

for example, barbituric acid derivatives, 1,4-benzodiazepines and meprobamate; diuretics such as, for example, chlorothiazide; cardiotonic agents such as, for example, digitalis products; agents which lower
5 blood pressure, such as, for example, hydralazine, dihydralazine, ACE inhibitors, prazosin, clonidine, rauwolfia alkaloids; agents which lower the fatty acid level in the blood, such as, for example, bezafibrate, fenofibrate; agents for thrombosis prophylaxis such as,
10 for example, phenprocoumon; anti-inflammatory substances such as, for example, corticosteroids, salicylates, or propionic acid derivatives such as, for example, ibuprofen; antibiotics such as, for example, penicillins or cephalosporins; NO donors such as, for
15 example, organic nitrates or sydnone imines.

Pharmaceuticals of the present invention can be administered orally, for example in the form of pills, tablets, film-coated tablets, sugar-coated tablets,
20 granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. The administration can, however, take place parenterally, for example subcutaneously,
25 intramuscularly or intravenously in the form of injection solutions or infusion solutions. Further suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal
30 therapeutic systems, or inhalational administration in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred mode of administration depends, for example, on the disease to be treated and its severity.

35

The medicaments according to the invention can be produced by the standard processes known for producing pharmaceutical products.

For this purpose, one or more compounds of the formula I and/or their physiologically acceptable salts, esters and hydrates are brought together with one or more solid or liquid pharmaceutical carriers and/or additives or excipients and, if desired, in combination with other active pharmaceutical ingredients with therapeutic or prophylactic action into a suitable administration form or dosage form, which can then be used as pharmaceutical in human medicine or veterinary medicine. The pharmaceutical products comprise a therapeutically or prophylactically effective dose of the compounds of the formula I and/or their physiologically acceptable salts, esters and hydrates, which normally amounts to from 0.5 to 90% by weight of the pharmaceutical product.

To produce, for example, pills, tablets, sugar-coated tablets and hard gelatin capsules it is possible to use lactose, starch, for example corn starch or starch derivatives, talc, stearic acid or salts thereof etc. Carriers for soft gelatin capsules and suppositories are for example fats, waxes, semisolid and liquid polyols, natural or hydrogenated oils etc. Examples of carriers suitable for producing solutions, for example injection solutions, or emulsions or syrups are water, physiological saline, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils etc. The compounds of the formula I and their physiologically acceptable salts, esters and hydrates may also be lyophilized, and the resulting lyophilizates can be used, for example, for producing products for injection or products for infusion. Examples of carriers suitable for microcapsules, implants or rods are mixed polymers of glycolic acid and lactic acid.

The pharmaceutical products may besides the active ingredients and carriers also comprise conventional additives, for example fillers, disintegrants, binders,

lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flavoring or aromatizing agents, thickeners, diluents, buffer substances, also solvents or solubilizers or
5 means to achieve a depot effect, salts to alter the osmotic pressure, coating agents or antioxidants.

The dosage of the active ingredient of the formula I to be administered, and/or of a physiologically acceptable
10 salt, ester or hydrate thereof depends on the individual case and should be adapted to the individual circumstances for an optimal effect in the conventional way. Thus, it depends on the nature and severity of the disease to be treated and on the sex, age, weight and
15 individual response of the human or animal to be treated, on the potency and duration of action of the compounds employed, on whether the therapy is acute or chronic or the aim is prophylaxis, or on whether other active ingredients are administered in addition to
20 compounds of the formula I. In general, a daily dose of about 0.01 to 100 mg/kg, preferably 0.1 to 10 mg/kg, in particular 0.3 to 5 mg/kg (in each case mg per kg of body weight) is appropriate on administration to an adult weighing about 75 kg to achieve the desired
25 effect. The daily dose may be administered in a single dose or, especially on administration of larger amounts, be divided into a plurality of, for example two, three or four, single doses. It may, depending on the individual characteristics, be necessary where
30 appropriate to deviate upward or downward from the stated daily dose. Pharmaceutical products normally contain 0.2 to 500 mg, preferably 1 to 200 mg, of active ingredient of the formula I and/or its physiologically acceptable salts.

35

The compounds of the formula I inhibit the various isoforms of NO synthase mainly through binding in the tetrahydrobiopterin binding cavity of the enzyme. Because of this property, they may be employed not only

as active pharmaceutical ingredients in human medicine and veterinary medicine but also as scientific tool or as aid for biochemical investigations in which such an inhibition of NO synthase is intended, and for
5 diagnostic purposes, for example in the in vitro diagnosis of cell samples or tissue samples. The compounds of the formula I and their salts, esters or hydrates may also be used as intermediates for preparing other active pharmaceutical ingredients.

10

Examples

The following preparation methods and examples illustrate the invention without restricting it:

15

2,6-Diamino-4-chloro-5-p-chlorophenylazopyrimidine

A solution of p-chloroaniline (25.5 g, 0.2 moles) in 6 N HCl (100 mL) was cooled to 0-5°C and then a solution of NaNO₂ (13.8 g, 0.2 moles) in water (40 ml)
20 was added dropwise with stirring. After completion of the addition, the solution was stirred for a further 15 min, and the progress of the reaction was checked with the aid of iodine/starch paper (blue coloration). The excess HNO₂ was destroyed by adding urea (5 g). The
25 diazonium salt solution was poured into a solution of 2,6-diamino-4-chloropyrimidine (26.0 g, 0.18 moles) in water (500 mL) and stirred for 30 min. Potassium acetate (70 g) was then added, and the mixture was stirred at room temperature for 16 hours. The
30 precipitated product was filtered off with suction, washed with H₂O and dried over P₄O₁₀ in a desiccator in vacuo. Yield: 44.0 g (81%) of yellow solid. Recrystallization from DMF/H₂O. m.p.: 268°C.

2,6-Diamino-4-alkylamino-5-p-chlorophenylazopyrimidines

General procedure:

A solution of 2,6-diamino-4-chloro-5-p-chlorophenylazo-pyrimidine (5.0 g, 16.6 mmol) and 10 g of the amine in DMF (50 mL) was stirred in an oil bath at 70°C for 5 hours. Addition of water (50 mL) was followed by cooling and filtering off the precipitate with suction, washing with water, drying and recrystallizing from EtOH or acetone/water.

The following were obtained in this way:

10

1.) 2,6-diamino-4-diethylamino-5-p-chlorophenylazo-pyrimidine, m.p.: 145-148°C

15

2.) 2,6-diamino-4-dibenzylamino-5-p-chlorophenylazo-pyrimidine, m.p.: 185-186°C.

3.) 2,6-diamino-4-(morpholin-4-yl)-5-p-chlorophenyl-azopyrimidine, m.p.: 219-221°C.

20

4.) 2,6-diamino-4-(piperidin-1-yl)-5-p-chlorophenyl-azopyrimidine, m.p.: 199-201°C.

5.) 2,6-diamino-4-(4-methylpiperazin-1-yl)-5-p-chlorophenylazopyrimidine, m.p.: 218-220°C.

25

2,5,6-Triamino-4-alkylaminopyrimidines (hydrochlorides)

General procedure:

30 A solution of 10 mmol of the 2,6-diamino-4-alkylamino-5-p-chlorophenylazopyrimidine in methanol (70 mL) and conc. ammonia (10 mL) was reduced in a shaking apparatus in the presence of the catalyst Raney nickel (3.5 g) under an H₂ atmosphere for 2 days. The catalyst
35 was filtered off under an argon atmosphere and the filtrate was evaporated to dryness in vacuo. The residue was treated with ether to remove the p-chloro-aniline, and the remaining solid was stirred with methanolic HCl (10%, 50 mL) overnight. The

dihydrochloride salt was filtered off with suction and dried over KOH in a desiccator in vacuo.

The following were obtained in this way:

- 5
- 6.) 2,5,6-triamino-4-diethylaminopyrimidine dihydrochloride, m.p.: 138-142°C
- 7.) 2,5,6-triamino-4-dibenzylaminopyrimidine dihydrochloride, m.p.: 165-167°C
- 10
- 8.) 2,5,6-triamino-4-(morpholin-4-yl)-pyrimidine dihydrochloride, m.p.: 215-218°C (decomposition)
- 15
- 9.) 2,5,6-triamino-4-(piperidin-1-yl)-pyrimidine dihydrochloride, m.p.: 238-242°C
- 10.) 2,5,6-triamino-4-(4-methylpiperazin-1-yl)-pyrimidine trihydrochloride, m.p.: 226-230°C (decomposition)
- 20

2-Amino-4-alkylamino-6-(R⁴)-pteridines

General procedure:

25

A solution of the arylglyoxal monoxime (7.5 mmol) containing the radical R⁴ in MeOH (10 mL) was added dropwise to a boiling solution of 2,5,6-triamino-4-alkylaminopyrimidine dihydrochloride salt (5 mmol) in

30

MeOH (20 mL), and this mixture was boiled under reflux for 3 hours. After cooling, the suspension or solution was adjusted to pH 9-10 with conc. ammonia, and the precipitate which separated out was filtered off with suction, washed with water and dried. The crude product

35

was recrystallized from EtOH and DMF/H₂O.

The following were obtained in this way:

- 11.) 2-amino-4-(dimethylamino)-6-phenylpteridine, m.p.:
247-250°C
- 12.) 2-amino-4-(dimethylamino)-6-(4-methylphenyl)-
5 pteridine, m.p.: 251-256°C
- 13.) 2-amino-4-(dimethylamino)-6-(4-methoxyphenyl)-
pteridine, m.p.: 280-284°C (decomposition)
- 10 14.) 2-amino-4-(dimethylamino)-6-methoxymethyl-
pteridine, m.p.: 237-239°C
- 15.) 2-amino-4-(diethylamino)-6-phenylpteridine
hydrate, m.p.: 203-205°C
- 15 16.) 2-amino-4-(diethylamino)-6-(4-chlorophenyl)-
pteridine dihydrate, m.p.: 250-254°C
(decomposition)
- 20 17.) 2-amino-4-(diethylamino)-6-(4-methoxyphenyl)-
pteridine hydrate, m.p.: 220-222°C
- 18.) 2-amino-4-(diethylamino)-6-(3,4-dimethoxyphenyl)-
pteridine hydrate, m.p.: 182-185°C
- 25 19.) 2-amino-4-(dibenzylamino)-6-phenylpteridine
dihydrate, m.p.: 225-227°C
- 20.) 2-amino-4-(dibenzylamino)-6-(4-chlorophenyl)-
30 pteridine dihydrate, m.p.: 250-253°C
- 21.) 2-amino-4-(dibenzylamino)-6-(4-methoxyphenyl)-
pteridine, m.p.: 245-247°C
- 35 22.) 2-amino-4-(dibenzylamino)-6-(3,4-dimethoxyphenyl)-
pteridine hemihydrate, m.p.: 200-201°C
- 23.) 2-amino-4-(di-n-propylamino)-6-phenylpteridine
trihydrate, m.p.: 177-178°C

- 24.) 2-amino-4-(di-n-propylamino)-6-(4-chlorophenyl)-
pteridine trihydrate, m.p.: 189-192°C
(decomposition)
- 5 25.) 2-amino-4-(di-n-propylamino)-6-(4-methoxyphenyl)-
pteridine hydrate, m.p.: 207-210°C (decomposition)
- 10 26.) 2-amino-4-(di-n-propylamino)-6-(3,4-dimethoxy-
phenyl)pteridine hydrate, m.p.: 158-160°C
- 27.) 2-amino-4-(morpholin-4-yl)-6-phenylpteridine
hydrate, m.p.: 224-227°C (decomposition)
- 15 28.) 2-amino-4-(morpholin-4-yl)-6-(4-chlorophenyl)-
pteridine hydrochloride hydrate, m.p.: 252-254°C
(decomposition)
- 20 29.) 2-amino-4-(morpholin-4-yl)-6-(4-methoxyphenyl)-
pteridine hydrochloride hydrate, m.p.: 238-240°C
(decomposition)
- 25 30.) 2-amino-4-(morpholin-4-yl)-6-(3,4-dimethoxy-
phenyl)pteridine trihydrate, m.p.: 218-220°C
(decomposition)
- 31.) 2-amino-4-(piperidin-1-yl)-6-phenylpteridine
dihydrate, m.p.: 209-211°C
- 30 32.) 2-amino-4-(piperidin-1-yl)-6-(4-chlorophenyl)-
pteridine dihydrate, m.p.: 245-247°C
(decomposition)
- 35 33.) 2-amino-4-(piperidin-1-yl)-6-(4-methoxyphenyl)-
pteridine hydrate, m.p.: 211-214°C (decomposition)
- 34.) 2-amino-4-(piperidin-1-yl)-6-(3,4-dimethoxy-
phenyl)pteridine hydrochloride dihydrate, m.p.:
238-241°C (decomposition)

- 35.) 2-amino-4-(4-methylpiperazin-1-yl)-6-phenyl-
pteridine hemihydrate, m.p.: 245-247°C
(decomposition)
- 5 36.) 2-amino-4-(4-methylpiperazin-1-yl)-6-(4-chloro-
phenyl)pteridine hemihydrate, m.p.: 277-279°C
(decomposition)
- 10 37.) 2-amino-4-(4-methylpiperazin-1-yl)-6-(4-methoxy-
phenyl)pteridine hemihydrate, m.p.: 228-230°C
(decomposition)
- 15 38.) 2-amino-4-(4-methylpiperazin-1-yl)-6-(3,4-di-
methoxyphenyl)pteridine dihydrate, m.p.: 148-151°C
(decomposition)
- 20 39.) 2-amino-4-(pyrrolidin-1-yl)-6-(4-methoxyphenyl)-
pteridine dihydrate, m.p.: 243-246°C
(decomposition)

**2-Amino-4-alkylamino-6-(R⁴)-5,6,7,8-tetrahydro-
pteridines**

25 General procedure:

A solution of pteridine (3 mmol) to be reduced in THF
(25 ml) was agitated catalytically with PtO₂ (0.10 g)/H₂
in a shaking apparatus until hydrogen uptake ceased.

30 The catalyst was filtered off, the filtrate was
evaporated to dryness, and the residue was treated with
methanolic HCl with stirring for several hours. The
crystals which formed were filtered off with suction,
washed with ether and dried in a desiccator in vacuo.

35

The following were obtained in this way:

- 40.) 2-amino-4-(morpholin-4-yl)-6-(4-methoxyphenyl)-
5,6,7,8-tetrahydropteridine hydrochloride hemi-
hydrate, m.p.: 219-222°C
- 5 41.) 2-amino-4-(morpholin-4-yl)-6-(3,4-dimethoxy-
phenyl)-5,6,7,8-tetrahydropteridine hydrochloride
hydrate, m.p.: 168°C
- 10 42.) 2-amino-4-(morpholin-4-yl)-6-phenyl-5,6,7,8-tetra-
hydropteridine dihydrochloride hemihydrate, m.p.:
200-203°C
- 15 43.) 2-amino-4-(piperidin-1-yl)-6-(4-chlorophenyl)-
5,6,7,8-tetrahydropteridine trihydrochloride
hydrate, m.p.: 170°C
- 20 44.) 2-amino-4-(piperidin-1-yl)-6-(4-methoxyphenyl)-
5,6,7,8-tetrahydropteridine trihydrochloride
hydrate, m.p.: 218-220°C
- 25 45.) 2-amino-4-(piperidin-1-yl)-6-phenyl-5,6,7,8-tetra-
hydropteridine dihydrochloride dihydrate, m.p.:
178-182°C
- 30 46.) 2-amino-4-(di-n-propylamino)-6-phenyl-5,6,7,8-
tetrahydropteridine trihydrochloride hydrate,
m.p.: 115°C
- 35 47.) 2-amino-4-(di-n-propylamino)-6-(4-methoxyphenyl)-
5,6,7,8-tetrahydropteridine dihydrochloride
dihydrate, m.p.: 120°C
- 48.) 2-amino-4-(diethylamino)-6-(4-chlorophenyl)-
5,6,7,8-tetrahydropteridine dihydrochloride hemi-
hydrate, m.p.: 138°C
- 49.) 2-amino-4-(cyclohexylmethylamino)-6-(4-chloro-
phenyl)-5,6,7,8-tetrahydropteridine dihydro-
chloride hydrate, m.p.: 160°C

The inhibition of the activity of purified nitric oxide synthase (NOS) by compounds of the general formula I can be determined as follows.

5

In this activity assay the L-citrulline which is a coproduct of the formation of NO by purified NOS is quantitatively measured. ³H-radiolabeled L-arginine is employed as substrate of the enzyme reaction and is converted into ³H-L-citrulline and NO. After completion of the enzyme incubation, generated L-citrulline is removed from unused L-arginine by ion exchange chromatography from the reaction mixture; the ³H activity measured by liquid scintillation then corresponds to the amount of L-citrulline, which is a direct measure of the activity of NOS.

15

The basic medium for carrying out the enzyme reaction is TE buffer (triethanolamine, EDTA, pH 7.0).

20

The final volume of each incubation is 100 µl. The reaction mixture is obtained by mixing the following 6 components on ice:

25

1. "REA-Mix" (pH 7.0) which contains triethanolamine, calcium chloride, magnesium chloride, EDTA, L-arginine, calmodulin and flavin adenine dinucleotide (FAD);
2. freshly prepared stock solution of β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH);
3. (6R)-5,6,7,8-tetrahydro-L-biopterin dihydrochloride stock solution (BH₄) or - for experiments without BH₄ - instead TE buffer;
- 35 4. purified NO synthase from pig cerebellum or from pig liver;
5. L-[2,3,4,5-³H]-arginine hydrochloride stock solution (1.526 TBq/mmol);
6. substance to be tested.

The final concentrations of the components in the incubation volume of 100 μ l are:

Triethanolamine 50 mM, EDTA 0.5 mM, CaCl_2 226 μ M, MgCl_2
5 477 μ M, L-arginine 50 μ M, calmodulin 0.5 μ M, FAD 5 μ M,
NADPH 1 mM, BH_4 (if added) 2 μ M, substance to be tested
100 μ M.

After mixing of the components on ice, the reaction
10 mixture was immediately incubated in a water bath at
37°C for 15 minutes. For determination of the IC_{50}
values it was incubated in the presence of 5 kU/ml
catalase for 45 minutes. After this incubation time,
15 the reaction was stopped by addition of 900 μ l of ice-
cold "stop buffer" (20 mM sodium acetate, 2 mM EDTA, pH
5.5), and the mixture (total volume now 1.0 ml) was
placed on ice. To remove the unreacted ^3H -L-arginine,
the mixture was loaded onto an ion exchange column with
0.8 ml of Dowex AG 50 WX-8 (100-200 mesh) which has
20 previously been washed and equilibrated with 2 ml of
stop buffer. After loading of the sample, the column
was eluted twice with 1 ml of water each time. The
flow-through of the sample and the eluate were
collected in scintillation vessels and purified (total
25 volume 3 ml). 9 ml of scintillator solution were added
to the 3 ml of aqueous measurement solution, and the
homogeneous mixture was measured in a Tricarb 2500 TR
(Packard) liquid scintillation counter for 1 minute for
each sample. The activity found with the substance to
30 be tested has been stated as a percentage of the
activity of the control. Each substance was tested for
an antagonistic effect in a concentration of 100 μ M in
the presence of 2 μ M tetrahydrobiopterin, and for an
agonistic effect on NOS in the absence of
35 tetrahydrobiopterin.

All incubations were carried out on triplicates. Each
experiment was repeated three times with different

enzyme preparations. Some results are indicated in the following Table 1.

Table 1

5

| Example | Remaining activity (% of V_{max}) | IC ₅₀ (μ M) |
|---------|---|-----------------------------|
| 11 | 92 \pm 11 | - |
| 12 | 15 \pm 7 | 75 |
| 13 | 13 \pm 4 | 74 |
| 15 | 75 \pm 3 | - |
| 16 | 42 \pm 10 | - |
| 17 | 2 \pm 0.1 | 45 |
| 18 | 23 \pm 4 | - |
| 19 | 0 \pm 0.05 | 3 |
| 20 | 0 | 3.5 |
| 21 | 0 \pm 0.05 | 5 |
| 22 | 0 | 2 |
| 23 | 77 \pm 16 | - |
| 24 | 7 \pm 4 | - |
| 25 | 25 \pm 12 | - |
| 26 | 0 | 39 |
| 27 | 41 \pm 8 | 82 |
| 28 | 3 \pm 1.5 | - |
| 29 | 5 \pm 0.1 | 34 |
| 30 | 5 \pm 3 | - |
| 31 | 0 \pm 0.05 | 62 |
| 32 | 3 \pm 1 | - |
| 33 | 7 \pm 0.2 | 50 |
| 34 | 0 | 44 |
| 35 | 83 \pm 1 | - |
| 36 | 64 \pm 9 | - |
| 37 | 84 \pm 5 | - |
| 38 | 99 \pm 16 | - |
| 39 | 30 \pm 5 | - |
| 40 | 66 \pm 14 | - |
| 41 | 68 \pm 11 | - |
| 42 | 51 \pm 3 | - |
| 43 | 0 | 13 |

WO 01/21619

- 32 -

PCT/EP00/08833

| | | |
|----|--------------|----|
| 44 | 0 | 42 |
| 45 | 0 | 6 |
| 46 | 8 ± 0.05 | - |
| 47 | 0 | 34 |
| 48 | 0 | 8 |
| 49 | 0 | 5 |

In addition, the relative selectivities of the antipterin inhibitors for the three known human NOS isoforms were measured. So doing, the IC₅₀ values for
 5 NOS-II/NOS-I and NOS-III/NOS-I were formed (compare Table 2).

The data show that the substances have an increased selectivity for inhibition of NOS-I relative to NOS-II
 10 and an increased selectivity relative to NOS-III.

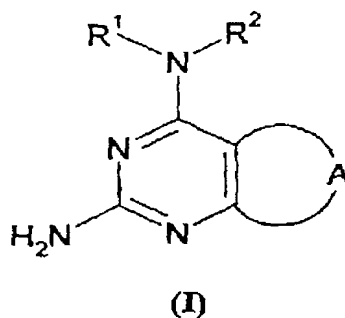
Table 2

| Substance Example | NOS iso- form | Activity (% of control) | IC ₅₀ (μ M) | Ratio NOS-II/I | Ratio NOS-III/I |
|----------------------|--------------------------------|---|----------------------------------|-------------------|--------------------|
| 21 | NOS-I NOS-II NOS- III | 27 \pm 1 81 \pm 6 68 \pm 2 | 18.7 400 ^a 100 | 21.3 | 5.3 |
| 45 | NOS-I NOS-II NOS- III | 0 \pm 0 50 \pm 2 11 \pm 1 | 22.0 81.5 14.2 | 3.7 | 0.6 |
| 46 | NOS-I NOS-II NOS- III | 1 \pm 0.1 68 \pm 1 27 \pm 0.2 | 18.7 200 ^a 53.4 | 10.7 | 2.9 |
| 47 | NOS-I NOS-II NOS- III | 0 \pm 0.1 78 \pm 0.4 31 \pm 3 | 7.4 250 ^a 63.6 | 33.8 | 8.6 |
| 48 | NOS-I NOS-II NOS- III | 2 \pm 0 74 \pm 4 27 \pm 1 | 41.5 300 ^a 45.4 | 7.2 | 1.1 |
| 49 | NOS-I NOS-II NOS- III | 0 \pm 0.1 78 \pm 6 18 \pm 1 | 4.9 200 ^a 36 | 40.8 | 7.3 |

^a Enzyme inhibition not complete up to 300 μ M (IC₅₀ values extrapolated).

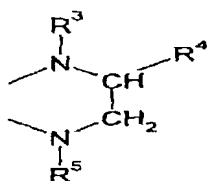
Patent Claims

1. Compounds of the formula I

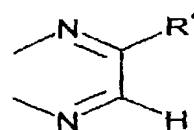


in which

A is a bridge of the formula



or



R^1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, aryl, alkylaryl or arylalkyl, where the organic radicals may be substituted by one or more substituents,

R^2 is, independently of R^1 , alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, aryl, alkylaryl or arylalkyl, where the organic radicals may be substituted by one or more substituents,

R^1 and R^2 may, together with the nitrogen atom bearing them, form a 3-8-membered ring which may optionally contain 0, 1 or 2 further heteroatoms from the series N, O, S and which is optionally substituted by one or more radicals,

R³ is hydrogen, -CO-alkyl, -CO-alkylaryl or -CO-aryl,

R⁴ is alkyl, alkenyl, alkynyl, cycloalkyl,
 5 cycloalkenyl, cycloalkylalkyl, aryl or alkylaryl,
 arylalkyl, -CO-O-alkyl, -CO-O-aryl, -CO-alkyl
 -CO-aryl, where the organic radicals may be
 substituted by one or more substituents,

10 R⁵ is, independently of R³, hydrogen, -CO-alkyl,
 -CO-alkylaryl or -CO-aryl,

R⁶ is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-
 (C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl,
 15 -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH,
 -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-
 alkyl, -SO₂-NR⁸R⁹,

R⁷ has, independently of R⁶, one of the meanings of
 20 R⁶,

R⁸ is hydrogen or alkyl,

R⁹ is hydrogen, alkyl or aryl,
 25

in all its stereoisomeric and tautomeric forms and
 mixtures thereof in all ratios, and its physiologically
 acceptable salts, hydrates and esters.

30 2. Compounds of the formula I as claimed in claim 1, in
 which

R¹ is hydrogen, (C₁-C₁₀)-alkyl, (C₃-C₈)-cycloalkyl,
 cycloalkylalkyl, aryl or (C₁-C₃)-alkylaryl or
 35 arylalkyl, where the alkyl radicals may be
 substituted by one or more substituents R⁶,

R² is, independently of R¹, (C₁-C₁₀)-alkyl, (C₃-C₈)-
 cycloalkyl, cycloalkylalkyl, aryl or (C₁-C₃)-

alkylaryl, where the alkyl radicals may be substituted by one or more substituents R^6 ,

5 R^1 and R^2 may, together with the nitrogen atom bearing them, form a 3-8-membered ring which may optionally contain 0, 1 or 2 further heteroatoms from the series N, O, S and which is optionally substituted by one or more R^6 radicals,

10 R^3 is hydrogen, $-\text{CO}-(\text{C}_1-\text{C}_7)\text{-alkyl}$, $-\text{CO}-(\text{C}_1-\text{C}_3)\text{-alkylaryl}$ or $-\text{CO-aryl}$,

R^4 is $(\text{C}_1-\text{C}_{10})\text{-alkyl}$, aryl or $(\text{C}_1-\text{C}_3)\text{-alkylaryl}$, $-\text{CO-O}-(\text{C}_1-\text{C}_5)\text{-alkyl}$, $-\text{CO-O-aryl}$, $-\text{CO}-(\text{C}_1-\text{C}_5)\text{-alkyl}$
15 or $-\text{CO-aryl}$, where the alkyl radicals may be substituted by one or more substituents R^7 ,

R^5 has, independently of R^3 , one of the meanings of R^3 ,

20 R^6 is $-\text{F}$, $-\text{OH}$, $-\text{O}-(\text{C}_1-\text{C}_{10})\text{-alkyl}$, $-\text{O-phenyl}$, $-\text{O-CO}-(\text{C}_1-\text{C}_{10})\text{-alkyl}$, $-\text{O-CO-aryl}$, $-\text{NR}^8\text{R}^9$, oxo, phenyl, $-\text{CO}-(\text{C}_1-\text{C}_5)\text{-alkyl}$, $-\text{CF}_3$, $-\text{CN}$, $-\text{CONR}^8\text{R}^9$, $-\text{COOH}$, $-\text{CO-O}-(\text{C}_1-\text{C}_5)\text{-alkyl}$, $-\text{CO-O-aryl}$, $-\text{S(O)}_n-(\text{C}_1-\text{C}_5)\text{-alkyl}$,
25 $-\text{SO}_2\text{-NR}^8\text{R}^9$,

R^7 has, independently of R^6 , one of the meanings of R^6 ,

30 R^8 is hydrogen or $(\text{C}_1-\text{C}_5)\text{-alkyl}$,

R^9 is hydrogen, $(\text{C}_1-\text{C}_5)\text{-alkyl}$ or phenyl,

35 aryl is phenyl, naphthyl or heteroaryl, all of which may be substituted by one or more identical or different substituents from the series halogen, $(\text{C}_1-\text{C}_5)\text{-alkyl}$ or phenyl, $-\text{OH}$, $-\text{O}-(\text{C}_1-\text{C}_5)\text{-alkyl}$, $(\text{C}_1-\text{C}_2)\text{-alkylenedioxy}$, $-\text{N}^8\text{R}^9$, $-\text{NO}_2$, $-\text{CO}-(\text{C}_1-\text{C}_5)\text{-alkyl}$,

-CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl,
-S(O)_n-(C₁-C₅)-alkyl, -SO₂-NR⁸R⁹,

heteroaryl is a 5- to 7-membered unsaturated
5 heterocycle which contains one or more heteroatoms
from the series O, N, S,

n is 0, 1 or 2,

10 in all its stereoisomeric and tautomeric forms and
mixtures thereof in all ratios and its physiologically
acceptable salts, hydrates and esters.

3. Compound of the formula I as claimed in claim 1, in
15 which

R¹ is hydrogen, (C₂-C₄)-alkyl which may be substituted
by one or more substituents R⁶, or (C₁-C₂)-
alkylaryl,

20 R² is (C₂-C₄)-alkyl which may be substituted by one or
more substituents R⁶, or cyclohexylmethyl or (C₁-
C₂)-alkylaryl,

25 or R¹ and R² form, together with the nitrogen atom
bearing them, a 5-7-membered ring which optionally
contains no or another heteroatom from the series N, O,
S,

30 R³ is hydrogen, -CO-(C₁-C₃)-alkyl or -CO-aryl,

R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, each of which
may be substituted by one or more substituents R⁷,

35 R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH,

R⁷ is -OH, (C₁-C₁₀)-alkyloxy, phenoxy or oxo,

aryl is phenyl, thienyl, furyl or pyridyl, each of which may be substituted by one or more substituents from the series (C₁-C₃)-alkyl, halogen, (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy, and

R⁸ and R⁹ have the meanings stated in claim 1,

in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios and its physiologically acceptable salts, hydrates and esters.

4. Compounds of the formula I as claimed in claim 1, in which

R¹ is arylmethyl and

R² is arylmethyl or cyclohexylmethyl,

or R¹ and R² form, together with the nitrogen atom bearing them, a pyrrolidine, piperidine, morpholine, dimethylmorpholine, thiomorpholine, or N-(C₁-C₂)-alkylpiperazine ring,

R³ is hydrogen,

R⁴ is alkyl or 1,2-dihydroxypropyl,

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH,

R⁷ is -OH, decyloxy and phenoxy,

aryl is phenyl which may be substituted by one or more substituents from the series (C₁-C₃)-alkyl, halogen and (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy, and

R⁸ and R⁹ have the meanings stated in claim 1,

in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios and its physiologically acceptable salts, hydrates and esters.

5. Compounds of the formula I as claimed in claim 1, which is a tetrahydropteridine in which R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, each of which may be substituted by one or more substituents R⁷.

6. Compounds of the formula I as claimed in claim 1, which is a pteridine in which R¹ and R² are alkyl and/or aryl, or in which R¹ is hydrogen and R² is cycloalkyl or cycloalkylalkyl, and in which R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, each of which may be substituted by one or more substituents R⁷.

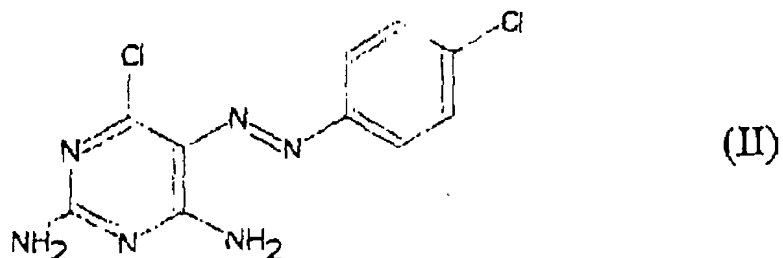
7. A pharmaceutical comprising a compound of the formula I as claimed in claim 1 in addition to conventional excipients and additives and optionally further active ingredients.

8. A pharmaceutical as claimed in claim 7 for the therapy and prophylaxis of strokes, pathological falls in blood pressure, in particular in septic shock and in cancer therapy with cytokines, ulcerative colitis, transplant rejection reactions, nephritis, reperfusion damage, infarct damage, cardiomyopathy, Alzheimer's disease, epilepsy, migraine and neuritis of varying etiology.

9. A pharmaceutical as claimed in claim 7 as inhibitor of NO synthase.

10. The use of the pharmaceutical as claimed in claim 9 for diagnostic purposes.

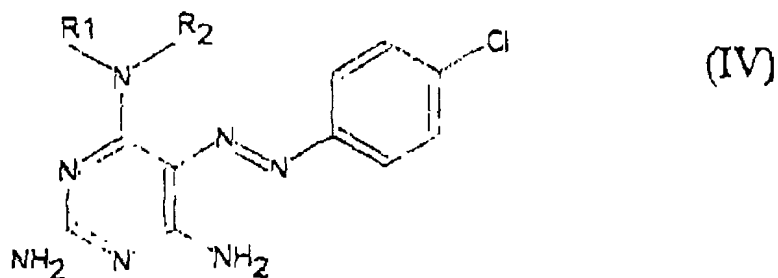
11. A process for preparing a compound of the formula I as claimed in claim 1, by reacting a compound of the formula II



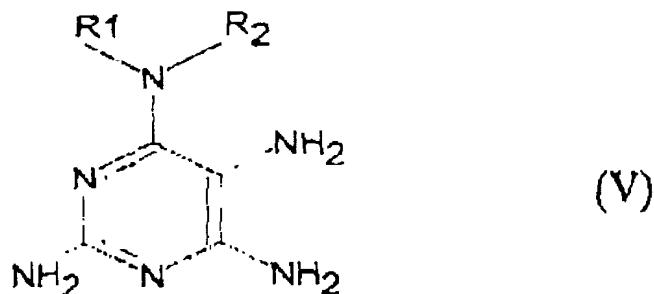
with a compound of the formula III



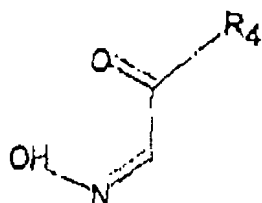
to give a compound of the formula IV



and converting the latter by catalytic hydrogenation into a compound of the formula V



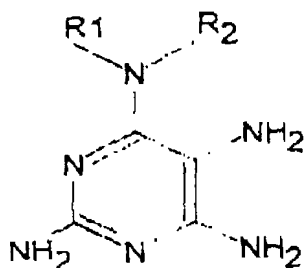
which is reacted with a compound of the formula VI



(VI)

to give a compound of the formula I, which can be converted by suitable derivatization, preferably acylation, into the desired compound of the formula I or its physiologically acceptable salts, hydrates, esters and adducts, and in which the substituents have the meanings stated in claims 1 to 3.

10 12. A compound of the formula V



(V),

in which R¹ and R² have the meaning defined in claim 1.

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG(19) Weltorganisation für geistiges Eigentum
Internationales Büro(43) Internationales Veröffentlichungsdatum
29. März 2001 (29.03.2001)

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A61K 31/519, A61P 9/00, C07D 239/50(71) Anmelder (für alle Bestimmungsstaaten mit Ausnahme
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(21) Internationales Aktenzeichen: PCT/EP00/08833

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tenstrasse 71, 78462 Konstanz (DE).

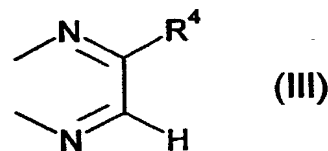
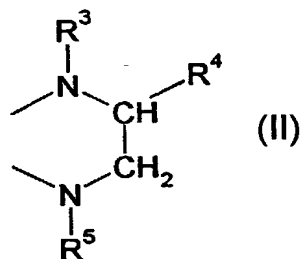
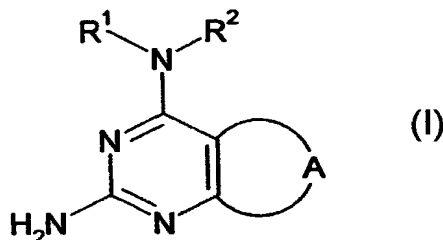
(25) Einreichungssprache: Deutsch

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(30) Angaben zur Priorität:
199 44 767.5 17. September 1999 (17.09.1999) DE(74) Anwalt: ACKERMANN, Joachim; Postfach 11 13 26,
60048 Frankfurt am Main (DE).

[Fortsetzung auf der nächsten Seite]

(54) Title: N-SUBSTITUTED 4-AMINOPTERIDINES, SYNTHESIS AND USE THEREOF AS PHARMACEUTICAL AGENT

(54) Bezeichnung: N-SUBSTITUIERTE 4-AMINOPTERIDINE, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE VER-
WENDUNG ALS ARZNEIMITTEL

(57) Abstract: Compounds of formula (I), where preferably: A = a bridge of partial formula (II) or (III), R¹ and R² = independently (substituted) alkyl, aryl or aralkyl, or together form a heterocycle, R³ = H, -CO-Alkyl, or -CO-Aryl, R⁴ = Aryl, -CO-O-Aryl or -CO-Aryl and R⁵ = H, are potent inhibitors of NO-synthase and are suitable as pharmaceutical agents for prophylaxis and treatment of disease states associated with a disturbed NO metabolism.

(57) Zusammenfassung: Verbindungen der Formel (I) in der bevorzugt A für eine Verbrückung der Form (II) ODER (III) steht, R¹ und R² unabhängig voneinander (substituiertes) Alkyl, Aryl oder Aralkyl oder zusammen einen Heterozyklus bilden, R³ für Wasserstoff, -CO-Alkyl, oder -CO-Aryl, R⁴ Aryl, -CO-O-Aryl oder -CO-Aryl und R⁵

[Fortsetzung auf der nächsten Seite]

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: N-Substituted 4-Aminopteridines, A Process For Their Preparation And Their Use As Pharmaceuticals the specification of which ☐ is attached and/or ☒ was filed on March 13, 2002 as United States Application Serial No. _____ and was filed as PCT International Application No. PCT/EP00/08833 on September 11, 2000.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate or § 365(a) of any PCT international application(s) designating at least one country other than the United States, listed below and have also identified below, any foreign application(s) for patent or inventor's certificate, or any PCT International application(s) having a filing date before that of the application(s) of which priority is claimed:

| Country | Application Number | Date of Filing | Priority Claimed Under 35 U.S.C. 119 |
|---------|--------------------|--------------------|---|
| Germany | 19944767.5 | September 17, 1999 | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| | | | <input type="checkbox"/> YES <input type="checkbox"/> NO |

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

| Application Number | Date of Filing |
|--------------------|----------------|
| | |
| | |

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application(s) and the national or PCT International filing date of this application:

| Application Number | Date of Filing | Status (Patented, Pending, Abandoned) |
|--------------------|----------------|---------------------------------------|
| | | |

I hereby appoint the following attorney and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.**, Customer Number 22,852, Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No. 20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilly, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewis, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M. Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33,921; James B. Monroe, Reg. No. 33,971; Doris Johnson Hines, Reg. No. 34,629; Allen R. Jensen, Reg. No. 28,224; Lori Ann Johnson, Reg. No. 34,498; David A. Manspeizer, Reg. No. 37,540; John Rissman, Reg. No. 33,764; M. Lawrence Oliverio, Reg. No. 30,915; Therese Hendricks, Reg. No. 30,389; and Anthony C. Tridico, Reg. No. 45,958. Please address all correspondence to **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.**, 1300 I Street, N.W., Washington, D.C. 20005, Telephone No. (202) 408-4000.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

| | | |
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| Full Name of Third Inventor FRÖHLICH, Lothar | Inventor's Signature X | Date X |
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| Full Name of Fourth Inventor KOTSONIS, Peter | Inventor's Signature <i>P. Kotsonis</i> X | Date 15/05/02 X |
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| Full Name of Fifth Inventor TAGHAVI-MOGHADAM, Shahriyar | Inventor's Signature X | Date X |
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| | | |
|---|--|--|
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| Full Name of Third Inventor FRÖHLICH, Lothar | Inventor's Signature <input checked="" type="checkbox"/> | Date <input checked="" type="checkbox"/> |
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